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Contents

PAGE

INSECT REPELLENTS, *J. Allen Scott* 3

CHEMICAL DESTRUCTION OF CIRCUMSCRIBED AREAS OF THE CENTRAL NERVOUS SYSTEM, *Glenn A. Drager, E. J. Poth, and E. B. Fernandez* 7

THE USE OF D- DESOXYEPHEDRINE IN NEUROPSYCHIATRY, *Don D. Jackson* 10

THE PRODUCTION OF NEURO-HYPERTENSION BY THE KIDNEY, *Eric Ogden, W. D. Collings, A. N. Taylor, and Eleanor Tripp* 14

SOME OBSERVATIONS ON THE EFFECTS OF A MIXTURE OF HIGH MOLECULAR ALKYL-DIMETHYLBENZYL AMMONIUM CHLORIDES OF VARIOUS INVERTEBRATES, *Charles H. Taft* 27

THE DISTRIBUTION OF SPECIES OF SANDFLIES, GENUS PHLEBOTOMUS, IN THE UNITED STATES AND THEIR RELATION TO THE TRANSMISSION OF LEISHMANIASIS, *Ardzroony Packchanian* 35

THE CONTACT SPLINT, *G. W. N. Eggers* 42

THE ORGANIZATION OF A HOSPITAL BLOOD BANK, *L. Jean Stubbins and William C. Levin* 46

SULFASUXIDINE AND SULFATHALIDINE, *Edgar J. Poth* 68

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INSECT REPELLENTS

J. Allen Scott*

The practicing physician, especially the pediatrician, has a professional interest in insect bites in addition to any personal interest which may be generated by the annoyance they cause him. Not only does he have to treat the secondary effects, such as infections due to scratching and alergic phenomena, but he also is frequently called upon for advice with regard to the prevention of insect bites. New insect repellents, more satisfactory than the older ones such as oil of citronella, and hitherto available only for military use, are now becoming available to the general public. Many persons are under the mistaken impression that DDT is one of these, and it should therefore be made clear that this substance does not drive insects away even though it does kill certain species under appropriate conditions.

Dr. W. E. Dove, Acting Chief of the Division of Insects Affecting Man and Animals, Bureau of Entomology and Plant Quarantine, U.S. Department of Agriculture, one of the men who has taken an active part in the development and testing of these chemicals during the war, has recently summarized the available information on some of the newer repellents. His address before the thirty-first annual meeting of the National Association of the Insecticide and Disinfectant Manufacturers has recently been published in a trade journal not usually seen by physicians (Dove, 1945). Some of the information contained in his article and in other publications may be of interest to the Texas medical public.

Repellents may affect the insect by two means. Some types must actually be touched by the insect in order to be effective, but others have an odor which acts on the sense organs of the insect. The latter type is more satisfactory, for if the insects must touch the skin before being driven away, they can still cause annoyance, and might mechanically transmit

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disease organisms. The chemicals which have an offensive odor for insects are not necessarily those which appear to man to have strong odors. On the other hand, creosote, which has an offensive odor for most people, does not in the least affect insects. Other substances are offensive to both man and insects and thus are not satisfactory. For example, extracts of vanillin or of the lotus flower will drive away blood-thirsty mosquitoes and cause them to lose all desire to feed for many hours, but the darkest night could not hide a person using such perfumes. Other chemicals having no odor detectable by man are good insect repellents, but they cannot be used because they are irritating or toxic when used on the skin.

Several government departments are testing new chemicals which will probably be even better than any now available, but three repellents which were developed for use by the armed forces are now on the market. One of these, dimethyl phthalate, was available before the war. Recent tests have shown that it is efficient as a mosquito repellent, and is especially effective against *Anopheles quadrimaculatus*, the principal carrier of malaria in the southern United States. It has also been successfully used as a repellent against chiggers or red bugs, which are of medical importance because in some parts of the world they are transmitters of tsutsugamushi disease, and everywhere may cause loss of sleep and pave the way for secondary infections. Military personnel have used this repellent against these mites by moistening the edge of the trouser cuffs, sleeves, and other openings of the clothing with it, or when they expect to be compelled to lie in infested grass, spraying it on the clothing has been found to be effective for a week. Against mosquitoes it is applied to the part of the skin which is exposed or covered only by thin clothing.

The second of these repellents is known by the trade name Indalone, and is reported to be composed of n-butyl mesityl oxide oxalate. This repellent is especially effective against biting flies, but is not very effective against the malaria mosquito of the United States.

The third repellent is known by the trade name, Rutgers 612, or National Carbon 612, and is reported to be composed of 2-ethylhexanediol-1,3. It was found to give a long period of complete protection against *Aedes aegypti,* the yellow fever mosquito, which is common in many parts of the United States, and which is also responsible for the transmission of epidemics of dengue fever. This repellent is also the most effective of the three against salt marsh mosquitoes.

In order to simplify the supplying of these repellents to the army, experiments were undertaken with mixtures of the three. The results were a surprise, for instead of having the average effectiveness against the different types, the mixture was as good against each type as any of the individual repellents in full strength. The mixture as supplied for military use became known as 6-2-2 or 1-1-1, depending upon the proportion of the different ingredients. Unless some of the repellents now being tested prove to be superior, these three chemicals will probably be the most satisfactory ones available on the post-war civilian market. It is believed that singly or as a mixture, they will replace most of the citronella and other essential oils which have been sold in the past. All of these repellents and their mixtures have been found safe to use on the skin and not injurious to clothing. Some of them have a dissolving effect on plastics and finger-nail polish, and may be irritating to the mucous membranes.

Experience in and around Galveston, Texas, with the 6-2-2 mixture when salt marsh mosquitoes are swarming about the person in large numbers has shown it to give remarkably effective protection, but it does have some limitations. It has been found that large numbers of these ravenous mosquitoes will readily attack the parts of the body to which the mixture has not been applied, even though covered with light layers of clothing. Moreover, it is well known that all repellents now available are less effective under conditions leading to profuse perspiration. It seems clear, however, that by carefully applying this preparation to all the exposed parts of the body, or perhaps spraying the clothing, one can protect himself against all of the insects of the Gulf Coast Region.

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CHEMICAL DESTRUCTION OF CIRCUMSCRIBED AREAS OF THE CENTRAL NERVOUS SYSTEM

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Surgical removal of various portions of the central nervous system in experimental animals has yielded much of our present understanding of the physiology and anatomy of the brain and cord. The extirpation of large superficial structures can usually be achieved with much accuracy. Small or buried areas offer more difficulties. The development of the sterotaxtic instrument is an improvement over surgical extirpation. Sterotaxtic equipment, however, is not available in most laboratories and its use requires considerable experience in order to obtain constant results.

Other investigations of chemical inhibition of regenerating peripheral nerves (Poth *et al.*, 1945) suggested that destruction of portions of the central nervous system might be more accurately and easily accomplished by injecting the desired region with a material that would not spread but which would effectively destroy the nervous tissue.

Such a method would be more accurate when applied to a small distinct area than would ordinary surgical removal, and yet it would not be so complex that it could not be used in any experimental laboratory.

METHODS

The motor cortex was chosen since the degree of destruction in this area is readily determined. Eight dogs were divided into two equal groups. Portions of the motor area were injected with 2 per cent gentian violet in one group and in the second control group the same amount of the motor cortex was surgically removed so that the effectiveness of the dye could be compared with extirpation and total destruction.

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The procedure of injecting the dye consisted of exposing the motor cortex in the usual manner under aseptic condition. The dura was sectioned without disturbing the underlying structures. Cotton, moist with saline, was packed around the area to be injected to prevent the spreading of the gentian violet over the surface of adjacent regions. The dye was injected with a No. 23 dull-pointed needle on a 1 cc. syringe. The syringe barrel was held in the manner of holding a pencil and the needle inserted approximately 2–3 mm. Usually the weight of the plunger forced enough dye into the tissue and seldom was it necessary to exert additional pressure. The needle was then withdrawn and reinserted a few millimeters from the previous site of injection until the area had been completely injected.

After recovery the animals were compared for degree of motor disfunction. Three weeks following the operation, the animals were sacrificed, perfused, and the brains and cords prepared to demonstrate degenerating nerve fibers (Swank and Davenport, 1935). The tissues were embedded in soft paraffin and sectioned at 50 micra.

Results and Conclusions

Both series of animals exhibited the same degree of pyramidal tract destruction.

Examination of the brain of the injected dogs showed a considerable amount of connective tissue growth in the meninges over the injected area, and usually the dura was firmly adherent to the underlying tissues. After fixation in 10 per cent formalin the brain was cut into slices of 3 or 4 mm. in thickness. The extent of the dye penetration was readily visible.

Histological preparations showed the same degree of degeneration in both groups of animals. This degeneration compared well with the amount of motor cortex destroyed and with the motor disfunction evident in the living animals.

When central nervous tissue is chemically destroyed the vessels of the pia need not be disturbed, eliminating troublesome bleeding and giving a clean field of operation. The area treated is also sharply outlined by the injected dye.

Although in this experiment the destruction of deep structures was not attempted, this technique should be applicable to deep nuclei. To destroy deep nuclei by ordinary surgical procedures it is usually necessary to injure or destroy superficial tissue. Obviously, this often introduces additional as well as undesirable variables into the experiment. By calculating the depth and angle of the deep structure, the area could be injected with considerable accuracy and without injuring the superficial tissue to any great extent. Subsequently the dye will mark the tissue destroyed and after fixation the exact area can be accurately determined.

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THE USE OF d- DESOXYEPHEDRINE IN NEUROPSYCHIATRY

A Preliminary Report

Don D. Jackson*

The purpose of this report is to present the results obtained by the administration of d- desoxyephedrine ("Desoxyn")† to 48 patients with various psychiatric and neurological syndromes. A detailed review of the pharmacology and chemistry of this drug has been offered by Ivy and Goetzl. This drug is very similar to amphetamine sulfate ("Benzedrine") in chemistry and physiological effect, although the dosage recommended is half that of amphetamine. However, it has been pointed out by Davidoff, by Simonson, and by Foltz, that in carefully controlled physiological testing (mostly on fatigue), d- desoxyephedrine is not quite equivalent to twice the dose of amphetamine. In general, an equivalent amount of desoxyephedrine will exert a somewhat more prolonged effect than amphetamine sulfate; usually from six to ten hours.

In this series the drug was given to patients with neurological or psychiatric disturbances who complained of extreme fatigue, somnolence or depression. Of some seventy patients selected on these criteria, forty-eight were carefully followed for four months or longer and make up the material for this report. The rest of the original group could not be evaluated because of inconsistency in taking the drug or by failure to return.

Materials and Methods

A total of 48 patients were studied. Fourteen of these exhibited major neurological symptoms while 34 were chiefly psychiatric. Among the neurological patients were 3 with

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†The Desoxyn was furnished through the courtesy of Dr. George E. Hazel of Abbott Laboratories.

multiple sclerosis, 6 with paralysis agitans, 1 with familial cerebellar ataxia, 2 with idiopathic epilepsy, 1 with Huntington's chorea, and 1 with narcolepsy. Among the psychiatric patients were 6 with reactive depression, 8 anxiety-tension states, 10 with mixed psychoneurosis in whom the chief complaint was fatigue, 4 in the depressed phase of manic depressive psychosis, 2 showing classical conversion hysteria and 4 with schizophrenia with depressive features.

All patients were started on 2.5 mg. of d- desoxyephedrine (one tablet) by mouth at breakfast and lunch. It was found that in most of the cases, this dosage produced slight or no effects, and consequently it was raised to 5 mg. twice daily. A few patients took an additional 5 mg. at 4:00 P.M. in order to maintain the effect through the evening. The patients with organic disease, and those in the depressed phase of a manic-depressive psychosis had the highest tolerance.

Almost all the patients found after two or three weeks that they had to increase their medication by 2.5 mg. or 5 mg. a day, in order to maintain the effect that the original dose produced. This tolerance was inexplicably absent in four psychiatric and two neurological patients. Furthermore, once the patient was taking a fairly large dose (15 mg. or more), the tolerance factor seemed to disappear.

Results

Neurological: The results in these cases were surprisingly gratifying. The patients with multiple sclerosis, Huntington's chorea and familial cerebellar ataxia, all reported improvement in their fatigue. Four of the six cases of paralysis agitans were similarly benefited, however, the other two reported no effect except an unpleasant "jitteryness." In addition, one woman with multiple sclerosis and one woman with familial ataxia reported relief from somnolence and improvement in motor difficulties. In the latter patient this could be demonstrated clinically. In another woman with multiple sclerosis, there was a reduction in nocturia from 10–15 times to 1–3 times. This remarkable improvement was maintained for three months when the drug was cut temporarily because she was losing too

much weight, and it was felt the medication was implicated. The case of narcolepsy responded satisfactorily to 5 mg. thrice daily. The two epileptics received 2.5 mg. thrice daily along with 30 mg. of phenobarbital and 0.1 gm. of "Dilantin." Desoxyephedrine acted as an analeptic in both of these patients who no longer complained of somnolence from the phenobarbital.

Psychiatric: The psychiatric cases that responded most satisfactorily to the medication were the reactive depressions. This is a similar result to the numerous articles that have been written using amphitamine sulfate in this condition. That there is a large element of suggestion in the treatment of fatigued psychoneurotics is borne out by the results with the two conversion hysterias. One patient's legs became stronger, and the other's stiff back disappeared. It was felt that since the patient can actually "feel" d- desoxyephedrine acting on him (increased heart rate, etc.), that it represents a useful medication for suggestive therapy. Perhaps this is the explanation for the total lack of beneficial results in the psychotic patients; the schizophrenic group did not receive a "lift" from the medication, and generally complained of "jitteryness"; the depressed psychotic patients were not discernibly affected in any way.

Discussion

There were few complaints of untoward side reactions in any patients except those exhibiting anxiety. It was a maxim that if a patient manifested obvious signs of anxiety, the drug would make him feel worse. Only two patients complained of mild gastric distress, but neither discontinued the medication. There were three patients who complained of insomnia although the last dose was taken at noon. In these cases, 0.1 gm. of a barbiturate overcame the difficulty. A fairly common complaint among the psychoneurotic patients was the "let down" feeling that occurred four to six hours after the last dose. It was not possible to overcome this entirely without causing insomnia, but in no case did the patient wish to discontinue therapy because of this factor.

Comparison with Amphetamine Sulfate ("Benzedrine"): Eight of the patients (one neurological and seven psychiatric) had received amphetamine sulfate in equivalent doses (5–10 mg.) previous to the administration of d- desoxyephedrine, and two patients were placed on amphetamine for several weeks after a month of d- desoxyephedrine. In no case did there seem to be a significant difference in substituting one for the other, except that it was noted that 2.5 mg. of desoxyephedrine did not always equal 5 mg. of benzedrine. Corroboratively, there were no differences reported between the two drugs by six normal subjects except that one person stated that benzedrine caused "heartburn" whereas desoxyephedrine did not.

Conclusion

The results obtained with d- desoxyephedrine ("Desoxyn") therapy in forty-eight neurological and psychiatric cases is reported. The cases were selected on the basis of a chief complaint of fatigue or somnolence. The relative effects of comparable doses of d- desoxyephedrine ("Desoxyn") were studied subjectively in eight patients and six normal persons, and it is felt there is little difference between the two medications.

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THE PRODUCTION OF NEURO-HYPERTENSION BY THE KIDNEY

ERIC OGDEN, W. D. COLLINGS, A. N. TAYLOR, AND ELEANORE TRIPP*

The Humoral Mechanism of Experimental Renal Hypertension. In 1934 Goldblatt[1] showed that dogs became hypertensive after partial occlusion of the renal arteries with a clamp.

This hypertension is humoral in origin. If one kidney of a dog be transplanted so that the femoral vessels and the ureter are the only connections to it,[2] and the other kidney be removed, clamping the femoral artery will affect the blood supply to the kidney and produce a rise of blood pressure as seen in Figure 1. This seems to be the best single proof of the humoral origin of this type of hypertension; but a wide variety of different experiments have been reported leading to the same conclusions.[3, 4, 5]

There is now general agreement as to the broad lines of the mechanism whereby this hypertension is produced. This field was recently reviewed by Braun-Menendez, Fasciolo, Leloir, Muñoz, and Taquini[5] and points adequately covered in that review are not further documented here. The clamp and other devices which lead to this type of hypertension cause the liberation of renin by the kidney. The only factor known to be common to these various methods of producing renal hypertension is the fact that in all of them the expansile pulsation[6] of the kidney is reduced or abolished. This is because the intrarenal pulse pressure is diminished by clamps or ties on the renal artery or aorta or because the kidney cannot expand adequately when it is splinted by perinephritis. Until some common factor is found other than diminished expansile pulsation this must be considered as a probable link in the chain establishing renal hypertension. Renin, a pseudoglobulin, enzymatically breaks down a circulating pseudoglobulin now

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known as "renin substrate ($\propto$2–globulin)", and releases angiotonin. Angiotonin is the immediate vasoconstrictor which appears to be responsible for the development of renal hypertension.

Angiotonin constricts most smooth muscle and acts independently of the autonomic nervous system.[8]

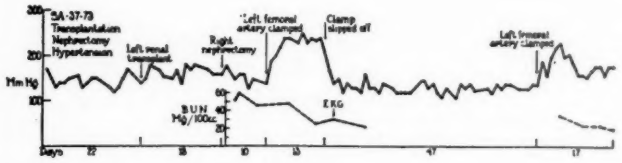

Figure 1: Hypertension from Transplanted Kidney (dog). Constriction of femoral artery; rise in blood pressure from 140 to 240 mm. Hg; blood pressure maintained at 240 mm. Hg for eight days, then sudden fall to 130 mm. Hg. Roentgenologic examination showed that the clamp had slipped off of the artery. Further constriction of the femoral artery; rise in blood pressure from 130 to 230 mm. Hg; return to 160 mm. Hg. Animal living and well four months after transplantation of the kidney.

Glen, F., Child, C. G., and Heuer, G. J.: Production of Hypertension by Constricting the Artery of a Single Transplanted Kidney, Ann. Surg., 106:848, 1937.

The relationship of this type of hypertension to the nervous system has been studied extensively. The production of hypertension by transplanted kidneys[2,3] and the fact that hypertension may be produced or persist after denervation of the kidneys or after extensive sympathectomy have made it evident that the nervous system plays no part in establishing this hypertension. This concept is further supported by all the work usually interpreted as indicating that the renin mechanism by itself is enough to account for most of the observations on renal hypertension.

It appears, however, that the evidence is not clear as to whether these observations are applicable to all species of animals or all stages of the disease. This doubt should be borne in mind when comparing experiments in animals in which hypertension is observed for a few years at most with the

diseases in man which are commonly studied after they have already been established for a long time.

It was early observed that this hypertension might appear in several forms varying in their chronicity, their intensity, and the incidence of complications.[9] Pregnancy,[10] fever and foreign protein reactions usually lower the blood pressure somewhat. Normal kidney tissue exerts some protective action against the hypertensive influence of kidney tissue whose pulsation is diminished. An animal with one renal artery clamped to a degree that will produce only a moderate hypertension or none at all may show a marked rise of blood pressure if the other kidney be removed.

Hypertension Maintained by a Different Mechanism. Very careful adjustment of the degree of occlusion, however, can produce hypertension from compression of only one renal artery in a fair proportion of animals, particularly in the rat; and the result of removing the affected kidney from the hypertensive rat has been studied.[11]

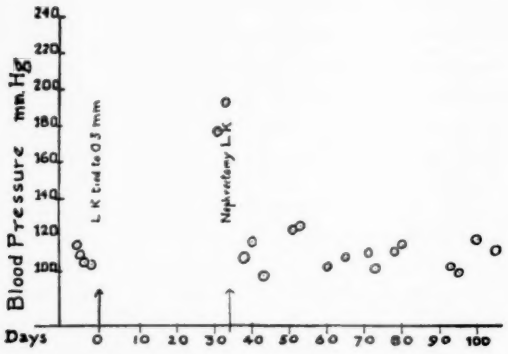

Figure 2: Complete relief of hypertension in the rat by removal of the pathogenic kidney after one month.

Patton, Henry S., Page, Ernest W., and Ogden, Eric: The Results of Nephrectomy on Experimental Renal Hypertension. Surg. Gyn. Obst., 76:493–497, 1943. By permission of Surgery, Gynecology and Obstetrics.

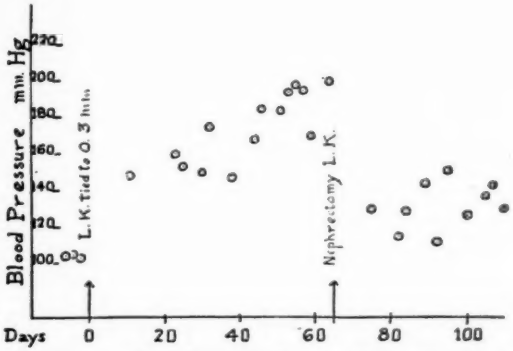

Figure 3: Moderate lowering of blood pressure by nephrectomy in rat with hypertension of two months' duration.

Patton, Henry S., Page, Ernest W., and Ogden, Eric: The Results of Nephrectomy on Experimental Renal Hypertension. Surg. Gyn. Obst., 76:493–497, 1943. By permission of Surgery, Gynecology and Obstetrics.

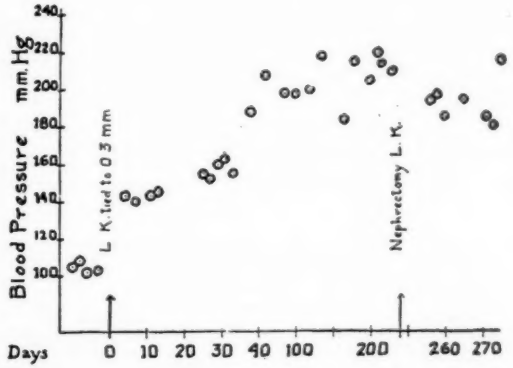

Figure 4: No lowering of blood pressure by nephrectomy after hypertension of seven months' duration. (Time scale has been altered to conserve space.)

Patton, Henry S., Page, Ernest W., and Ogden, Eric: The Results of Nephrectomy on Experimental Renal Hypertension. Surg. Gyn. Obst., 76:493–497, 1943. By permission of Surgery, Gynecology and Obstetrics.

The rat whose blood pressure is plotted in Figure 2 was definitely hypertensive after partial ligation of the left renal artery. Removal of the left kidney 34 days after the ligation was followed by immediate return of the blood pressure to the original level. Figure 3 shows that another hypertensive rat, allowed to keep the offending kidney 65 days after the hypertension was first produced, failed to recover completely as judged by its level of blood pressure after the kidney was removed. Figure 4 illustrates a similar experiment; but in this case the left kidney was removed 7 months after the hypertension was established and there was practically no fall of blood pressure.

TABLE I

The Relation of Duration and Severity of Hypertension to the Effectiveness of Nephrectomy in Rats.

		Result of Nephrectomy		
Duration of hypertension—weeks	No. of Animals	No change or a rise	Lowered, but not to Normal	Return to Normal
5–10	21	2	9	10
11–45	26	13	11	2
TOTALS	47	15	20	12
Severity of hypertension—mm. of Hg				
140–160	26	12	9	5
161–180	11	2	6	3
181–200	7	1	3	3
Over 200	3		2	1
TOTALS	47	15	20	12

(Note that there is no evident relationship between the maximum blood pressure level and recovery.)

Patton, Henry S., Page, Ernest W., and Ogden, Eric: The Results of Nephrectomy on Experimental Renal Hypertension. Surg. Gyn. Obst., 76:493–497, 1943. By permission of Surgery, Gynecology and Obstetrics.

Table I summarizes such experiments on 47 rats and shows that the rat whose affected kidney is removed within ten weeks may be expected to return to its pre-operative blood pressure level, whereas hypertension of longer duration tends to be permanent.

These experiments lead to three important conclusions. Since rats with long-standing hypertension are unaffected by a procedure which regularly cures newly hypertensive rats, there must be a change* in the mechanism which keeps the blood pressure elevated as the duration of the disease increases. Since nephrectomy fails to alter the long established hypertension this must be maintained by a means independent of the affected kidney. Since nephrectomy completely cures the newly hypertensive rat, the other (non-renal) mechanism, which is so apparent later, is not operating at this time.

The Effect of Nembutal on the Maintenance of Hypertension. Since the mechanism maintaining chronic experimental hypertension of renal origin differs from that which institutes it, studies have been made of this sustaining mechanism.[12] Rats made hypertensive by partial ligation of the renal artery received enough Nembutal to produce narcosis and anesthesia. The blood pressure of rats which had been hypertensive for a long while returned to normal. Such a dose of Nembutal did not lower the blood pressure of newly hypertensive rats, so it seems likely that the hypertension in the two groups is sustained by different mechanisms. This experiment, summarized in Table II, again shows a definite distinction between the newly hypertensive rat and the rat with hypertension of long standing (compare experiments 1 and 2, Table II) and points strongly towards the nervous system which Nembutal chiefly affects.

Yohimbine. Reed, Sapirstein, Southard and Ogden also tested hypertensive rats with yohimbine hydrochloride. Yohimbine has been tried clinically as an aphrodisiac and as an antihypertensive agent and is known to block the action of the sympathetic nervous system and to reverse the action of epinephrine. Yohimbine lowered the blood pressure in hypertensive rats with hypertension of long standing but not in newly hypertensive rats. (Compare experiments 10 and 12, Table II.)

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*This important conclusion was first clearly stated by Sapirstein[12] on different evidence.

TABLE II

The Response of the Systolic Pressure of Normotensive and of Early and Late Hypertensive Rats to Nembutal, Picrotoxin, and Yohimbine.

Exp. No.	No. of Animals	Dosage (mg/kg)		Remarks	Type of Animal	Blood Pressure in mm. Hg Average for Groups Before	After	Diff.	Range of Diff.
1	24	40	Nembutal	Anesthetized	Late	169	115	**—54**	—104 to —22
2	25	40	Nembutal	Anesthetized	Early	151	145	**— 6**	— 24 to 43
3	12	40	Nembutal	Anesthetized	Control	119	113	**— 6**	— 23 to 14
4	5	20	Nembutal	Non-anesthetic dose	Late	175	163	**—12**	— 23 to 1
5	5	40	Nembutal	Resistant to anesthesia	Late	176	160	**—16**	— 18 to — 6
6	37	3	Picrotoxin	Convulsions	Control	123	127	**4**	— 8 to 11
7	7	4.5	Picro. and 40 Nemb.	Quiet. All reflexes present	Control	127	120	**— 7**	— 12 to 4
8	9	3	Picrotoxin	Convulsions	Late	168	177	**9**	3 to 15
9	9	4.5	Picro. and 40 Nemb.	Quiet. All reflexes present	Late	177	170	**— 7**	— 20 to — 1
10	20	3	Yohimbine		Late	161	135	**—26**	— 45 to —13
11	12	3	Yohimbine		Control	120	127	**7**	— 1 to 15
12	12	3	Yohimbine		Early	152	153	**1**	— 22 to 11

Column 5: Early hypertensive, less than two weeks; late hypertensive, more than two months.

Blood Pressure measured by tail plethysmograph method.

Reed, Racheal, Sapirstein, Leo A., Southard, Frank D., Jr., and Ogden, Eric: The Effects of Nembutal and Yohimbine on Chronic Renal Hypertension in the Rat, American Journal of Physiology, 141:707, 1944.

Jacobs and Yonkman[13] lowered the pressure of three out of four hypertensive dogs by giving yohimbine. It is hoped that before long a more detailed report will be available from Yonkman's laboratory on a larger number of dogs and that an attempt may be made to look for correlation between the duration of the hypertension and the effect of yohimbine.

Yohimbine is not only a sympatholytic agent but also a centrally acting pressor substance. In this connection it should be noted[14] that an intravenous dose of 0.5 mg./kg. yohimbine hydrochloride, just enough to abolish or slightly reverse the effect of epinephrine on the blood pressure of a dog anesthetized with cyclopropane, affects the blood pressure transiently if at all; but such a dose accelerates the heart and markedly raises the blood pressure of unanesthetized dogs. Yonkman used 20 mg./kg. by mouth. He recognized in these experiments that large doses produce profound hypotension. The foregoing discussion of some of the pharmacological vagaries of this substance is a caution. Even though Yonkman's results appear to show that the hypertensive dog behaves like the hypertensive rat, yet the uncertainties of such a drug demand that evidence be accepted as convincing only from experiments which are designed to check the particular point in question and which have surely avoided or controlled possible errors due to the peculiarities of reactions to the drug.

TABLE III

Effects of F 883 and F 933 on Systolic Blood Pressure of Normal and Late Hypertensive Rats.

Description	No. of Rats	Systolic Pressure, mm. of Hg		
		Before Inj.	After Inj.	Difference
F 883 (5 mg/rat)				
Late Hypertensive	16	165	126	—39
Normal	8	117	115	— 2
F 933 (10 mg/rat)				
Late Hypertensive	16	151	144	— 7
Normal	8	121	119	— 2

Sapirstein, Leo A., and Reed, Racheal K.: Effects of Fourneau 883 and Fourneau 933 on Late Hypertension in the Rat, Proc. Soc. Exp. Biol. and Med., 57:135, 1944.

Other Sympatholytic Agents. The dioxane derivatives studied by Fourneau, particularly F 933 (piperidino-methyl-benzo-dioxane) and F 883 (diethyl-amino-methyl-benzo-dioxane) have been widely used for pharmacological analysis. Like yohimbine, F 883 is both sympatholytic and adrenolytic; but F 933 is only adrenolytic.[15, 16] As the effects of these drugs are somewhat variable it is necessary to show in each instance that the dose used is really producing the effect desired. These drugs have been applied by Sapirstein and Reed[17] to the problem in hand but at present it has not been possible to control the doses in individual animals with the accuracy which this type of analysis demands for real certainty. However, as far as their analysis goes, it seems that F 933, the purely adrenolytic drug, was without important effect on any of their animals, whereas F 883, the sympatholytic drug, lowered the blood pressure of the rats of longstanding hypertension and not that of the normotensive rats (Table III). This is in accord with the observations on yohimbine.

As previously discussed, there are many experiments from which authors have concluded that experimental renal hypertension is purely humoral in the mechanism of its establishment and quite independent of the nervous system in origin. Of these experiments many are clearly of short duration by their very nature or are shown to be short by the protocols. For the rest, it should be borne in mind that so long as no suggestion as to a possible change of mechanism had been made it was natural for an investigator to proceed with his experiments *as soon as* he had established hypertension in his animal. We have not found any experiments published which seem to bear on the point of this discussion though personal communications[18, 19] have suggested that some workers have made observations which should warn against assuming that the hypertensive dog of several years' standing reacts like the rat of several months' hypertension.

These experiments all point toward the conclusion that the mechanism sustaining hypertension, once it is long established, is mediated by the sympathetic nervous system in contrast to the well-understood mechanism which starts experimental renal

hypertension and which is known to be independent of the sympathetic nervous system.

Conclusive evidence on the question is not available. Further experimental work is under way and the critical experiment on this point is yet to be designed. But the concept is supported by many indirect experiments.

Other Animal Experiments. Dock[20] observed that when he pithed the spinal cords of rabbits made hypertensive by ligatures around the renal arteries, their blood pressure fell to the same low level as that of normotensive pithed rabbits. He argued that had the hypertension been due to a circulating pressor substance it would have continued to act even after destruction of the spinal cord. It is interesting that he reported these rabbits as having been hypertensive for months and thus offers some support to the concept that animals made hypertensive by a renin-releasing mechanism may later appear to be purely neuro-hypertensive.

Dell'Oro and Braun-Menendez[21] and Dexter and Haynes[22] have detected renin circulating in the blood of newly hypertensive animals but failed to detect it after the hypertension had become well established. An early disagreement between Houssay[23] and Mason[24] as to whether pressor substances in the blood of Goldblatt animals could be detected by means of the Lowen-Trendelenberg frog preparation may now be resolved. The hypertensive animals used by Houssay were newly established and those used by Mason had been hypertensive for several months.[25]

Observations on Man. There is good evidence that the renin-angiotonin system is not usually operating in chronic essential hypertension[26] in man and that the nervous system[27] plays an important part. On the other hand renin has been demonstrated in the blood stream of patients with acute glomerulonephritis.[28]

The exact sequence of events is still controversial and it is possible that some phase of essential hypertension may prove to have important features in common with the type of neuro-hypertension here discussed. Of the many reports evaluating experimentally the parts played by the nervous system and the kidneys respectively in patients with hypertensive diseases

none claim to deal with newly established essential hypertension. Diagnosis and classification of hypertension in man is rarely completed in cases definitely known to be in the early stages. The hypertensive patient who reports a long past history of acute glomerulonephritis (in which the renin mechanism is now clearly established), of hypertensive toxemia of pregnancy or of many bouts of systolic hypertension with anxiety is perhaps one in whom the past elevation of blood pressure is etiologically concerned with the present hypertensive disease. The neuro-hypertension which afflicts the rat after renal hypertension is in this respect somewhat similar to essential hypertension.

In spite of the uncertainty of the evidence on some points just discussed it seems beyond reasonable doubt that renal hypertension in the rat undergoes *a profound change in mechanism with the passage of time.* Such an observation is of practical value even if it serves only to remind us of the possibility that different phases of human hypertensive disease in the same individual may have fundamentally different mechanisms.

Summary. The humoral mechanism of experimental renal hypertension is reviewed briefly. The effects of removal of the restricted kidney from rats with unilateral renal hypertension and of the administration of Nembutal, yohimbine and F 883 are discussed. All of these techniques elicit different responses according to the duration of the hypertension. It is concluded that the early renal humoral phase of experimental hypertension in the rat is replaced by a sympathetically mediated neuro-hypertension. This point of view is examined in the light of pertinent information available concerning experimental hypertension in other species and naturally occurring hypertension in man.

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SOME OBSERVATIONS ON THE EFFECTS OF A MIXTURE OF HIGH MOLECULAR ALKYL-DIMETHYL-BENZYL AMMONIUM CHLORIDES ON VARIOUS INVERTEBRATES

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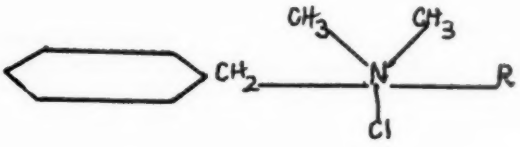
In recent years many quaternary ammonium compounds have been introduced as cationic antiseptics or disinfectants. One of these, a mixture of high molecular alkyl-dimethyl-benzyl ammonium chlorides,† has attracted considerable attention. Its general structural formula is:



R. represents the alkyl radicals C_8H_{17}, $C_{10}H_{21}$, $C_{12}H_{25}$, $C_{14}H_{29}$, $C_{16}H_{33}$ and $C_{18}H_{37}$. The source of these radicals is a mixture of fatty acids of coconut oil in original proportions. Insomuch as these fatty acids in coconut oil occur in constant proportions, this relationship holds in the final product resulting in a preparation of uniform composition.

This mixture is freely soluble in water, soluble in acetone and alcohol, slightly soluble in benzol and insoluble in ethyl

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†This material in 12.8%, 0.1% aqueous solution and 0.1% tincture is sold by the Winthrop Chemical Company under the trade marked name of "Zephiran Chloride" brand of Benzalkonium Chloride Refined for use as an antiseptic or germicide for surgical procedures and a 10% aqueous solution is sold under the trade marked name of "Roccal" brand of Benzalkonium Chloride for use as an industrial antiseptic or disinfectant. The Winthrop Chemical Company generously furnished the Benzalkonium Chloride used in these Experiments. In these experiments Zephiran Chloride and Roccal were used interchangeably and no difference was observed in their action on invertebrates.

ether. The aqueous solution is slightly alkaline to litmus. It possesses an aromatic odor and foams like soap on shaking. Aqueous solutions have an acrid taste which disappears as dilutions increase (Heinman, 1937). When diluted for topical application the aqueous solution has wetting, detergent, keratolytic, emulsifying and emollient properties. The surface tension of a 1:1000 solution in distilled water is 37.4 dynes/cm. at 25.3° C. (Walter, 1938). It has the property of forming invisible, nonperceptible films on surfaces. These films are quite durable and protect the organisms under them (Miller, Abrams, Huber and Klein, 1943). Sevag and Ross (1944) have studied the mechanism of the inhibitory action on yeast and think that there is an inhibition of the cytochrome-cytochrome oxidase of the yeast cells.

It was introduced as a surface antiseptic and disinfectant by Domagk (1935), and its bacteriostatic, bacteriocidal and fungicidal properties have been described by Dunn (1936, 1937, 1938), Thompson et al. (1939), Miller and co-workers (1939), and many others. Valko and DuBois (1945), Rawlins, Sweet, and Joslyn (1943), Epstein, Harris, and Katzman (1943), Kolloff, Wyss, Himelick, and Mantele (1943), and many others have reported on the chemical constitution and biological activity of groups of related compounds.

Walter (1938) used a 1:200 solution as the only source of fluid for guinea pigs for three months. There was an initial fall in weight and a diarrhea. The cavies then gained weight and there was no sign of abnormalities at the end of three months when the animals were killed and the tissues examined. He also administered 1 cc. of a 1:1000 solution intraperitoneally daily for three months. One female gave birth to a healthy litter. On autopsy there was no gross pathology except scattered areas of thickening and scarification of the abdominal parietes. Walter (1938) determined the twenty-four hour M. L. D. intraperitoneally at 2 mg./100 gms. as 1:1000 or 1 mg./100 gms. as 10%. Histological examination of liver, kidney, and intestines showed no changes which could be interpreted as manifestations of systemic toxicity. Maier (1939) showed that dilutions up to 1:4000 caused little or no

reaction when applied to the cornea of an albino rabbit. He also suggested that it might be a useful preservative for biological fluids.

Taft (1945) showed that dilutions up to 1:150,000 stopped the isolated heart of *Limulus polyphemus* in systole and that the action was irreversible. Taft and Strandtmann (1945) stated that under laboratory conditions a 1:100,000 solution prevents hatching of eggs and kills all stages of the larva and pupae of *Culex quinquefasciatus*, 1:250,000 kills first and second instar larvae of this mosquito, dilutions up to 1:1,000,000 reduce the number of larvae. A 1:100,000 solution kills first, second, and third instar larvae of *Aedes aegypti*. 1:250,000 kills about 80% of the first instar larvae and prevents maturity of the remainder.

Pomerat, Emerson, and Taft (unpublished), attempted to show the effect of this antiseptic on the metamorphosis of the barnacle, *Balanus*. The cyprid larvae were immersed in solutions, ranging from 1:10,000 to 1:800,000 in sea water. There was very little interference with metamorphosis. Solutions of from 1:10,000 to 1:25,000 seriously interfered with the normal development of the adult, and in most cases there were grave abnormalities. Those immersed in solutions up to 1:200,000 showed bright refractive vacuoles, resembling fat inclusions. These showed very few if any feeding movements and died within a short time. Those placed in dilutions of 1:400,000 or greater were not materially affected.

As it has been suggested that this quaternary ammonium compound might be useful in mosquito control, it seems advisable to study its effects on some of the forms with which it would come in contact if used for this purpose. This report is limited to its action on invertebrates. The solutions of this chemical were made in the type of water in which the organism tested normally lives, so there would be no confusion of results by diluting the native habitat with distilled water.

The action of this mixture on protozoa seems to depend at least in part on the fluidity of the endoplasm and the rigidity of the cortical plasm. The reactions of *paramecia* are very marked. When a drop of culture and a drop of the 1:500,000

solution are brought edge to edge (making a 1:1,000,000 dilution) there is not an immediate complete mixing of the two fluids. A front of the drug seems to gradually invade the drop of culture. *Paramecia* swimming about freely touch the edge of the front and immediately withdraw (very similar to their reaction to acid) when they are engulfed by the antiseptic solution, their movements slow down, the trichocysts are shot out and the extruding contractile vacuole extrudes more than normally. When it bursts, the fluid inner protoplasm of the *paramecia* flows out and the animal disintegrates. This cycle of events occurs in about one minute in a dilution of 1:100,000 and in about fifteen minutes with a dilution of 1:1,000,000. *Colpidium*, being another form with relatively fluid endoplasm and flexible ectoplasm, responds in a similar manner.

In a mixed culture containing various species of *hypotriches* the response is somewhat similar to that of *paramecia*. Shortly after exposure the oral cilia become unusually active, the trichocysts are discharged and the contractile vacuoles become very prominent. Death occurs in six minutes with a dilution of 1:100,000 and in twenty minutes with 1:1,000,000.

With *euglena* the picture is somewhat different. Not only are these organisms more resistant to this mixture of high molecular alkyl-dimethyl-benzyl ammonium chlorides than the cilates, but when they die there is not complete disintegration as there is with the infusoria tested. When *euglena* are exposed to a dilution of 1:20 there is an immediate loss of motility and form, and all are dead in one minute. The chloroplasts are clumped in the center. In 1:20,000 solution the *euglena* begin to lose motolity and to assume a spherical shape in about two minutes. In ten minutes there is almost complete loss of motility, and in twenty minutes there is no motility of any kind, even in the contractile vacuoles. The chloroplastids begin to separate into strands. In twenty-five minutes the cell walls begin to rupture. In a 1:50,000 solution there was some motility at the end of three and a half hours; all were dead in nineteen hours. In a 1:100,000 there was some motility at the end of nineteen hours. In the 1:50,000 and 1:100,000 solutions the *euglena* had a tendency to form spherical shapes as they

do in old cultures. In all work with protozoa and rotifers the slides were kept in moist chambers to avoid any danger of their drying.

A mixed culture of *rotifers* was exposed to a 1:20 solution. There was immediate cessation of all vital activities. Dilutions up to 1:100,000 killed *rotifers* in under two hours, the time depending on the strength of the solution, and up to 1:1,000,000 killed them in nineteen hours.

Some *amphipoda* were placed in solutions of 1:100,000, 1:200,000 and 1:400,000. They were all dead in a few hours. At least some species of *Cyprids* are quite resistant to this drug. Those immersed in a 1:20,000 solution remained very active for more than five hours when the drop began to dry up.

When *planaria* are placed in a 1:1000 solution they struggle violently for a short time. There is complete loss of motion in less than two minutes and they become covered with a white film. They start to disintegrate in four minutes and there is complete loss of form in eleven minutes. In a 1:100,000 solution of *planarians* are decidedly uncomfortable. They squirm about a great deal and try to crawl out of the watch-glass. In about twenty minutes a white film begins to cover them. In one hour there is no activity. Some assume bizarre shapes and they float around in the dish. In about four hours they have become blobs of protoplasm.

A few experiments were performed with dog *ascaris*. When the worms were placed in a 12.8% solution they became stiff and showed no signs of life within six minutes. In a 1:1000 solution in thirty minutes the worms were dead. In 1:10,000 up to thirty minutes there was response to stimuli, touching with a glass rod. At the end of ninety minutes, the worms did not respond when placed in warm water. In 1:50,000 the worms responded to warm water after ninety minutes exposure and were alive eighteen hours later. Higher dilutions did not materially affect the worms.

The annelid worm *Enchytrae albidus* will live for a week or so in a 0.6% to 0.9% solution of sodium chloride. Distilled water seems to be fatal to them in a few hours. The solutions of the quaternary ammonium compound used in these experiments on them were made up in 0.9% sodium chloride. In

a 1:10,000 solution the worms struggle violently at first, but quiet down in about eight minutes. Their peristaltic activity is still present. In fifteen minutes there is no sign of life. There is no noticeable effect on the cuticle. These worms were then washed and replaced in 0.9% sodium chloride. There was no sign of recovery. Solution up to 1:1,000,000 kills these worms in four hours or less, depending on the concentration.

Some small *starfish* were placed in an aerated 1:8000 solution in sea water. In eight minutes they responded by curling the ends of their arms. In an hour and fifteen minutes all motion in the ambulacral feet had ceased. Starfish placed in aerated 1:400,000 solution were all dead within twenty-four hours. *Fundulus* and snails *(Nassa obsoleta)* in the same container were apparently normal.

Several experiments were performed with the *gastropod crepidula.* If *crepidulae* are placed in a finger bowl with aerated sea water, and after they have become attached to the bottom of the bowl, sufficient of the drug is added to make a 1:2500 solution, the *crepidulae* are loose and dead in fifteen minutes. In 1:8000, similar results are obtained in one hour. When 0.1 cc. of a 1:10 solution is dropped on the head and foot of a *crepidula,* all response from these organs to stimuli ceases immediately. The tissues to which this strength is applied, appear cooked. When other *crepidulae* are immersed upside down in a 1:1000 solution, in five minutes the feet and tentacles appear swollen; in ten minutes they are covered with mucous. The response to touching becomes less and less, and finally ceases in fifty minutes.

Limulus polyphemus is not a particularly favorable subject for this type of work, as except for the sense of smell, it is difficult to tell when they are dead. An arbitrary standard was used, i.e., when there was no movement of the appendages when the ventral surface was stroked. Small (about three inches long) *limulus* were injected with 0.1 cc. of a 1% solution. In about four and a half hours there was no response to stimuli. The animals were autopsied and with the exception that the heart had stopped beating, the viscera were essentially normal. Small *limulus* placed in aerated finger bowls of 1:2000

in sea water were alive and apparently normal in twenty-four hours.

The actions of a mixture of high molecular alkyl-dimethyl-benzyl ammonium chlorides on members of different phyla of the invertebrates have been shown. There is a difference in the reaction of various invertebrates to these materials. This is not a phylogenetic difference but seems to be due to the type of protective covering with which the animal is provided. In general those with a rigid and more or less impermeable coating are less affected than those with a flexible permeable covering. This suggests that the action of this mixture on these animals is due to a large part to its ability to lower surface tension and to its wetting properties. Its power of forming invisible surface films undoubtedly plays a part in its action.

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THE DISTRIBUTION OF SPECIES OF SANDFLIES, GENUS PHLEBOTOMUS, IN THE UNITED STATES AND THEIR RELATION TO THE TRANSMISSION OF LEISHMANIASIS

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It is generally accepted that both cutaneous and visceral leishmaniasis are transmitted chiefly by various species of sandflies, genus *Phlebotomus*.† The available evidence indicates that there are no endemic areas of leishmaniasis in regions where the sandflies do not exist. The development of leishmania parasites, the change from aflagellar to flagellar forms, takes place in the stomach and proboscis of sandflies. The disease has been successfully transmitted by the bite of sandflies to the hamster. Recently there have been human experiments in which *Phlebotomus* infected with *Leishmania donovani* were allowed to feed on five human volunteers from an area where kala-azar did not occur, with the result that all five volunteers contracted the disease; thus establishing beyond question that sandflies *Phlebotomus* are vectors of leishmaniasis (Chandler, 3; Knowles, 10; Strong, 18; Swaminath, Shortt, and Anderson, 19; Wenyon, 20, 21).

Up to the present, no endogenous cases of leishmaniasis have been reported in the United States. However, from time to time, sporadic cases of exogenous cutaneous and visceral leishmaniasis have been diagnosed in this country; as the number of exogenous cases are gradually increasing, the question arises whether or not indigenous species of *Phlebotomus* and dogs may some day become infected from these cases and thus establish

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†At present, it is controversial as to whether the correct spelling of the genus is *Phlebotomus* or *Flebotomus* (Kirby, 9; Mangabeira, Filho, and Galindo, 12), but the matter is under consideration by the International Commission on Zoological Nomenclature (Hemming, 7). The writer prefers to use the form *Phlebotomus* because it conforms to the files of the majority of references, particularly that of the Medical Index.

leishmaniasis in the United States (Munter and Packchanian, 13; Packchanian, 15).

This communication is a study of the species of sandflies, *Phlebotomus* that are found in the United States and their relation to the transmission of leishmaniasis.

Species of Sandflies, Genus Phlebotomus, Found in the United States

The sandfly, *Phlebotomus*, is a midge-like *Diptera* measuring from 1.5 to 3.5 mm. It is a greyish-brown or buff colored slender insect with a hairy body, very long and lanky legs, and narrow, hairy wings. Each wing possesses nine longitudinal veins extending to the edge of the wing; the latter is a distinguishing feature of the genus. They have long, slender antennae, and a proboscis longer than the head which projects beyond the tip of the labium when at rest.

The eggs are laid by the females in cracks in masonry, etc., and hatch within six to nine days to caterpillar-like larvae, whose last abdominal segments have two pairs of long bristles projecting vertically upward in a fan-like manner. The larvae feed on organic debris and within two to eight weeks develop into pupae which metamorphose into adults after six to ten days. The small size of the adult sandflies enables them to pass readily through the meshes of mosquito nets.

The life span of the adult approximates fifteen days. Its power of flight is limited to a range of about 46 meters. Females of most of the species feed almost exclusively on blood at night; the males feed on decayed organic matter. *P. anthophorus*, reared in the laboratory, apparently feed only in the mornings. At times, *Phlebotomus* are confused with another blood-sucking midge, the *Culicoides*. The detailed taxonomic descriptions and keys for identification and differentiation of various species of the genus *Phlebotomus* are found in entomological literature (Addis, 1; Chandler, 3; Dyar, 5; Knowles, 10; Root, 16).

A review of the literature and a search in various American museums revealed that at least six species of sandflies, *Phlebotomus*, are found in the United States (See Table No. I).

TABLE I

The Species of Sandflies (Phlebotomus) in the United States

Species of Phlebotomus	Authority	Data Available	
		Distribution	Habitat
P. anthophorus	Addis, 1945	Texas	Collected on rabbits. Feeds also on hamster in laboratory.
P. diabolicus	Hall, 1936	Texas	Attacks man
P. limai	Fonseca, 1935	Alabama Georgia North Carolina	Collected from a hollow tree near Florence, Alabama, by Dr. L. E. Rozeboom
P. stewarti	Mangabeira and Galindo, 1944	California	Found in burrows of ground squirrels
P. texanus	Dampf, 1938	Texas	Found in nest of *Atta texana* (ants)
P. vexator	Coquillett, 1907	California Louisiana Maryland Virginia	In Virginia found feeding on black snakes; in California in burrows of ground squirrels

REMARKS: At least two other unpublished species of sandflies exist in the United States, personal communications (2). It is probable that additional species, as yet unrecognized, may be found; this remains to be investigated.

1. *Phlebotomus anthophorus* was first observed by Brundrett during the summer of 1944 at Uvalde, Texas. The morphological and biological characteristics of this species were studied and described in 1945 by Addis, who also collected the specimens of this sandfly from rabbits and rabbit pens at Uvalde and reared them in his laboratory at Houston, Texas. *P. anthophorus* appears to feed only in the morning, never having been found feeding after sundown. In captivity, it

shows a preference for rabbits, but will feed on hamsters; efforts to have them feed on rats and humans so far have been unsuccessful (Addis, 1).

2. *P. diabolicus*, was first described by Hall in 1936. This species, so far, is found only in Texas and is known to attack man (Hall, 6).

3. *P. limai* has recently been collected from a hollow tree in the vicinity of Florence, Alabama, by Dr. L. E. Rozeboom. Other specimens of this species have been collected at Rockingham, North Carolina; Clinton, Mississippi; and Selma, Alabama. These are preserved in the U. S. National Museum, Washington, D.C., and the Natural History Museum of Chicago, Illinois. The specimens examined by Dr. Rozeboom are apparently identical with the South American species of *P. limai* first described by Fonseca in 1935; however, additional taxonomic studies on the specimens of this species collected in the United States is desirable. *P. limai* is found also in Georgia and possibly in Florida (Stone and Wetmore, 2; Rozeboom, 17).

4. *P. stewarti* was described by Mangabeira and Galindo in 1940. The specimens of this species of sandfly were collected in the burrows of ground squirrels in California (Mangabeira, Filho, and Galindo, 12).

5. *P. texanus* was described by Dampf in 1938 and represents the third species of sandfly found in Texas. Specimens of this species were collected from ant nests *(Atta texanus)* in San Antonio, Texas (Dampf, 4).

6. *P. vexator* was first collected in the United States by H. G. Barbar in 1898, who found the insect engorged with blood under the scalings of black snakes at Plummers Island, Maryland (Barbar, 2). This species, however, was later described by Coquillett in 1907 and for many years was thought to be the only species of *Phlebotomus* in the United States. *P. vexator* is apparently widely distributed in the United States. Specimens of this species have been found in California, Louisiana, Maryland, and Virginia. Usually this species is associated with snakes; however, those recently collected in California were found with *P. stewarti* in the burrows of ground squirrels (Barbar and Stone, 2; Mangabeira, Filho, and Galindo, 12).

It is probable that additional species of *Phlebotomus*, as yet undiscovered, may be found in the United States (Dampf, 4). While *P. anthophorus*, *P. diabolicus*, and *P. texanus* so far have been reported only in Texas, and *P. stewarti* only in California, these states are not necessarily the only localities where these and other species of sandflies may be present.

The Transmission of Leishmaniasis by Phlebotomus

Leishmaniasis is transmitted chiefly by sandflies, genus *Phlebotomus*. Many species of sandflies are known to have been infected naturally or experimentally with *Leishmania donovani* or *L. tropica* in numerous localities in the Eastern hemisphere and in Latin America (Knowles, 10; Strong, 18; Swaminath, Shortt, and Anderson, 19; Wenyon, 20, 21). As yet, it has not been determined whether the species of sandflies which exist in the United States are capable of transmitting leishmaniasis. This important problem remains to be investigated under rigid experimental conditions. However, from numerous experimental data of several investigators, it seems that all the species of *Phlebotoumus* so far investigated are vectors of leishmaniasis and in all probability the species found in the United States may also represent potential vectors for transmitting leishmaniasis.

Within the past year, four exogenous cases of leishmaniasis have been diagnosed in the United States and 499 cases of the cutaneous form have been reported in American soldiers in the Near East area. Since the incubation period of leishmaniasis is sometimes a matter of months and even years, it is apparent that cases may develop clinical symptoms after their arrival in this country. An increase in the incidence of exogenous leishmaniasis in the United States therefore, is likely to occur as a result of an increment in travel of civilian and military personnel from areas where the disease is endemic (Munter and Packchanian, 13; Packchanian, 15).

Dogs infected with *Leishmania* act as reservoirs for cutaneous and visceral leishmaniasis (Chandler, 3; Strong, 18). Recently it has been demonstrated that some species of rodents, particularly gerbels *(Rhombomys opimus)* and souslike *(Spermophilopsis leptodactylus)* in Middle Asia, are naturally infected

with *Leishmania* and act as reservoirs for cutaneous leishmaniasis. The infection is transmitted from animal to animal, and from animal to man by sandflies, *Phlebotomus*, (Hoare, 8; Latyshev and Kriukova, 11; Wenyon, 21).

Although many American entomologists are aware that *Phlebotomus* exist in certain areas of the United States, this fact is not widely known to physicians, public health officers, and epidemiologists. It is desirable that our health officers institute the necessary measures to safeguard *Phlebotomus* and dogs from contact with exogenous cases of leishmaniasis. This is essential to prevent the establishment of leishmaniasis in the United States.

Summary

The geographic distribution in the United States of six species of sandflies, genus *Phlebotomus*, has been enumerated and the potential danger of their acquiring and transmitting leishmaniasis to man and dog has been pointed out. It is suggested that epidemiologists, clinicians, and health officers be alert to prevent the contact of dogs and sandflies with exogenous cases of leishmaniasis.

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THE CONTACT SPLINT

G. W. N. Eggers*

The internal fixation of fractures with metal plates has been in a period of improvement for a number of years. With the advent of the nonelectrolytic metals, the problem was considered as solved by many. However, this unfortunately has not been a fact. Many cases of plate fixation result in nonunion or delayed union; and, in some cases, the plates have broken. The cause of such failures is physiologic.

The basic observation in all fractures is that the damaged ends of the bones undergo aseptic necrosis and absorption. In the closed treatment of fractures, the muscular pull keeps the reduced fracture ends in constant contact. The placing of a fixed plate on a fracture so completely immobilizes the bones that the absorbed bone ends are actually kept separated by the plate (Fig. I). This results in nonunion or delayed union which we see so frequently reported in various surgical journals.

*From the Department of Surgery, Orthopedic Division, The University of Texas School of Medicine, Galveston, Texas. Received for publication January 30, 1946.

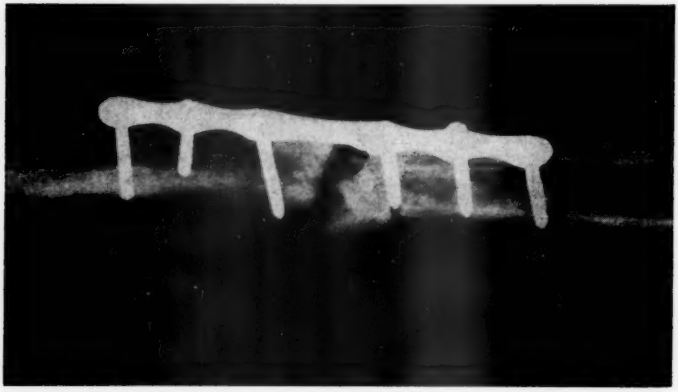

Fig. I—Usual type of plate fixation showing absorption of ends of fractured fragments due to aseptic necrosis.

The purpose of the contact splint is to provide controlled mobility of the fractured bones. In cases requiring internal fixation, this slotted type of plate is used not in absolute fixation as a plate usually is, but by controlled fixation to the bone, permitting longitudinal motion. Thus the fractured ends are in constant contact, as in a closed reduction, due to the muscular pull in the long axis of the bone (Fig. II). This is conducive to a better callous formation.

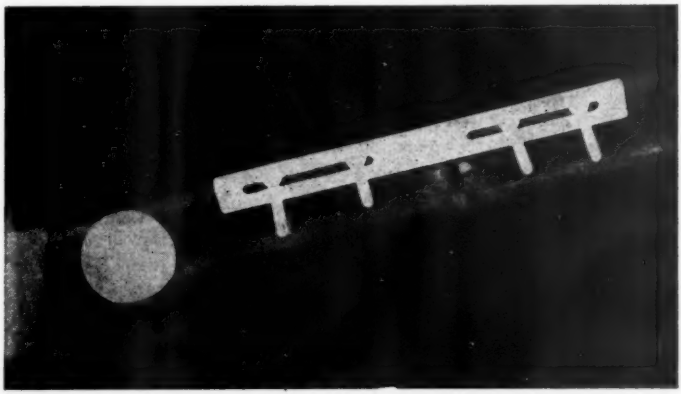

Fig. II—The contact splint allows controlled longitudinal motion which keeps the ends of the fragments in constant contact as absorption of the aseptic necrosis occurs.

The plate is held in position by four screws placed as distant from the fractured ends as practicable. The screws are not tight, and the plate can be moved in a longitudinal direction which thus permits constant contact of the fractured ends. The shape of the plate keeps the screwheads countersunk, and the L-shaped edges increase its strength (Fig. III).

The illustrations of Fig. IV and V show operative appearance of splint after application. Note the interval between the fractured ends when anatomic traction is placed on the leg and

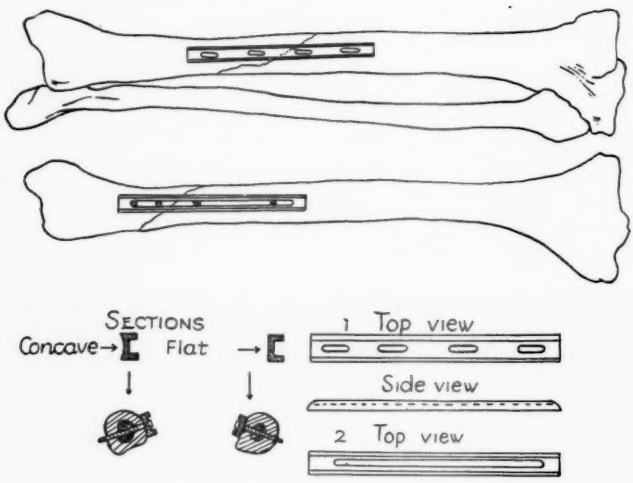

Fig. III—Diagrammatic views of splint.

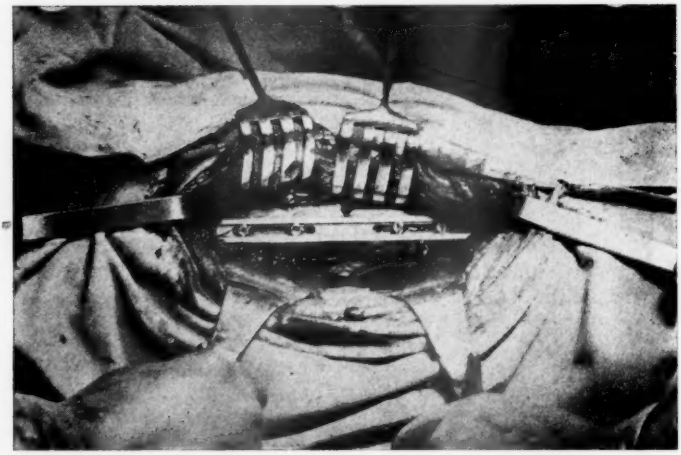

Fig. IV—Application of plate showing space between fragments in traction.

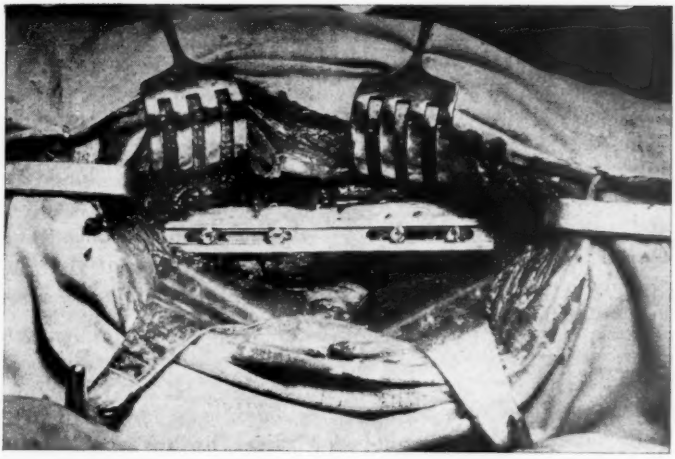

Fig. V—Traction released and fragments return to contact which persists due to muscular pull.

the return to contact of the fractured ends when the traction force is released.

It is hoped the contact splint will promote better results in the internal fixation of fractures requiring such surgical treatment.

THE ORGANIZATION OF A HOSPITAL BLOOD BANK*

L. Jean Stubbins and William C. Levin

The success of any laboratory depends upon a great number of correlated routine procedures. The personnel should be well supervised and trained; the laboratory procedures should be simple and readily performed; the results should be accurate and easily interpreted, and the final reports should be clear and concise. At no time should any laboratory permit itself to become so routine that new techniques and procedures are overlooked for the sake of economy.

Personnel

The personnel of a hospital blood bank is an important item in its success. There should be a Medical Director who assumes all duties regarding contact between the blood bank staff and the hospital physicians. The Medical Director sanctions all procedures outlined by the Technical Director and also interprets all untoward results.

The Technical Director should be a Registered Medical Technologist trained in all blood bank procedures. She assumes all responsibility as to the actual mechanics of the blood bank. She does all of the supervising of the personnel and relieves the Medical Director of all responsibilities regarding techniques. All technical assistants should be Registered Medical Technologists.

Because of the tremendous amount of clerical work connected with blood banks, a capable secretary is indispensable. Her personality should be pleasant, kind, coöperative and understanding. She interviews all prospective donors and records their temperature and hemoglobin on their cards. She keeps all records, handles all correspondence and all telephone calls.

It is not desirous to have individual staff members set up their transfusions when the day staff has gone. This leads to

*From the Blood and Plasma Bank, The John Sealy Hospitals, The University of Texas, Galveston, Texas. Received for publication February 8, 1946.

many possible errors and it is wise to have this tremendous responsibility placed on a few well-trained people rather than on numerous unskilled ones.

Laboratory assistants and maids are employed to prepare, clean and autoclave all equipment used in the administration of blood and intravenous fluids. They assume the responsibility of keeping the blood bank clean and orderly, of maintaining a constant source of supplies and are equipped to assist with donors if any untoward syncopal reaction occurs.

Physical Demands

The physical demands of a blood bank necessitate adequate space. There should be a comfortable and "friendly" waiting and reception room for prospective donors. The secretary's desk and telephone are in this room. A small table is equipped with sterile thermometers and equipment for doing hemoglobin tests.

The donor room contains the beds and bedside tables. The bedside tables are covered with clean linens. Alcohol sponges, tincture of mercresin and 1% novocaine are on this table. The sphygmomanometer, scissors, sterile donor sets, sterile hypodermic syringes and needles are also placed here. This room must be airy and light with a convenient closet for clean linens.

The laboratory should be spacious, well ventilated and light. Overcrowding and confusion should be eliminated by permitting only technicians in this room. The equipment must be orderly and placed conveniently. The kitchen should have adequate water facilities as the initial washing of equipment is done in this room. Supply shelves, neat and orderly, are also in this room.

General Operative Procedure

Any blood bank requires a constant source of fresh blood. Of course, family donors make up the greatest supply. Any patient receiving 500 cc. of blood is asked to repay this blood with one donor. Ward patients are never charged for blood not replaced. However, private patients are charged $25.00 a pint if blood is not replaced. This money is then given to the

professional donor who is called in to replace this blood. This method is extremely satisfactory both to the private patient and the blood bank. Many of our patients live hundreds of miles from Galveston and are charity patients. In this instance, we call upon our local Red Cross Chapter and various volunteer organizations to send in donors for this patient. These organizations are extremely dependable and coöperative.

Our rules and regulations governing our operative procedures are strictly adhered to in all circumstances. All persons are rejected as donors who:

1. have a history of syphilis.
2. have a history of malaria.
3. have a history of recent illness or infection.
4. have a history of allergy.
5. have a temperature elevation of 1 degree or over.
6. have a hemoglobin of under 70%. (Sahli method.)
7. have eaten or drunk anything except water within the six hours prior to giving blood.
8. are under 18 years of age or beyond 60 years of age. Donors under 21 must have written parent's permission to act as donors.
9. are underweight; men must weigh 110 lbs. and women 115 lbs. as a minimum.
10. have given blood within the last two months.

(All mothers who wish to act as donors must have a minimum nine month post-partum period.)

The problem of allergic reactions, consisting of urticaria and the rare possibility of allergic shock has been practically erased from our records by rejecting all allergic donors. The sensitivity in the donor can be transmitted passively to the patient by means of transfusion. This sensitivity, when transferred passively into the patient, can last for a period as long as three months. Also, we must secure a fasting donor as the patient might be allergic to certain foods ingested by the donor and an allergic reaction will be demonstrated in the patient. This has been discussed completely by Wiener (1943).

Our immediate concern in blood transfusions is to benefit the patient. However, we cannot overlook the fact that healthy donors must be secured. We must protect our donors as carefully as we protect our patients.

Donors with low hemoglobins are rejected for obvious reasons. The donor would necessarily suffer and the patient would not be benefited by a low volume of erythrocytes. A rise in temperature of 1 degree in our donors is a reason for rejection as systemic and upper respiratory infections, all virus infections and other illnesses can be transmitted by transfusion. Furthermore, the withdrawal of blood from a donor who has an elevated temperature is definitely contraindicated from the standpoint of the donor's health. All donors who have a history of tuberculosis are definitely rejected.

No person with a history of syphilis or who subsequently has a positive serology on testing is accepted as a donor. The tremendous hazard of transmitting syphilis by blood transfusion deserves serious consideration and emphasizes the necessity of rigid regulations to obviate this unfortunate accident. Frazier and Pian (1939) advise the above procedure as do Kilduffe and DeBakey (1942).

Malaria is the next most important disease transmitted by transfusion. The infection may be latent for years and still be transmissible. Jankelson (1931), Naveiro (1934) and Wright (1928) have reported cases of malaria resulting from the transfusion of blood from donors who had been symptomless from 33 to 37 years.

Rare accidents of other diseases which have been transmitted by blood transfusion are influenza, relapsing fever, measles, smallpox, septicemia, staphlococcus septicemia and typhoid fever. Thus a complete exoneration of symptoms in donors must be secured by careful inquiry. We will accept donors only between the ages of 18 to 60. After the age of 60 blood regeneration is generally retarded.

Men must weigh 110 pounds and women must weigh not under 115 pounds. This weight limit is demanded as blood volume corresponds to body weight.

The above rules and regulations are printed on slips which are on all wards in the hospital. Thus prospective donors who do not meet our requirements are eliminated as donors before coming to the blood bank.

Transfusion Reactions

Any hospital that has a transfusion service is faced with the problem of blood transfusion reactions. These are divided into three types; namely, the pyrogenic reaction, the urticarial or allergic reaction and the hemolytic reaction.

Pyrogenic Reactions

These reactions, caused by faulty technique, occur too often in the average hospital to be excused. The clinical description of this type of reaction is one which is easily recognized. During the transfusion or immediately thereafter the patient may experience a chill with a rapid rise in temperature. This fever may persist for 5 or 6 hours and then subside without treatment. Lack of care in the preparation of blood transfusion equipment and of the fluids employed is responsible for most pyrogenic reactions. In any event, the transfusion must be discontinued as these symptoms may cloak the possibility of the much graver hemolytic type of reaction. Changes of personnel will often precipitate a series of pyrogenic reactions due to inexperience. Contamination of equipment before the transfusion must be avoided. There is no therapy required for this type of reaction.

Urticarial Reactions

The use of fasting and non-allergic donors will enable the average hospital to reduce their incidence of this type of reaction. Little is known about this type of reaction except that it will occur even when the most stringent caution is observed. The urticaria or edema is indeed not serious but extremely uncomfortable. However, every precaution must be taken to avoid edema of the larynx. The choice of therapy in these reactions is epinephrin hydrochloride, 0.5 cc. (1-1000 solution) injected subcutaneously.

Hemolytic Reactions

This is the type of reaction that is prevented by extreme care and caution in performing compatibility tests. The responsibility of the technician is paramount in this procedure. There is never any excuse for a hemolytic reaction to occur as this reaction is the result of transfusing incompatible or hemolyzed blood. The patient will complain of chilliness, fever, constriction behind the sternum and severe pain in the lumbar region. When red blood cell destruction has been extensive, the patient may go into shock with cold, moist skin, air hunger and lowered arterial pressure. Death may occur at this stage if shock therapy is not instituted immediately.

To diminish the occurrence of blood transfusion reactions and fluid infusion reactions is the *sine qua non* of any transfusion service. The initial procedure to reduce the rate is to exercise scrupulous and meticulous care in the laboratory, in the cleaning of equipment and in the actual mechanics of administration. In our hospital we have printed forms for both transfusion and infusion reaction reports. These are placed on every ward and the nurses are responsible for making written reports whenever a reaction occurs. These reports are investigated by the blood bank and an accurate summary of their incidence is maintained.

Our total reaction rate is now 0.485% as of December 1, 1945. This includes an overall rate of 1,865 blood transfusions, 406 plasma transfusions and 5,560 fluid infusions.

JOHN SEALY HOSPITAL
Blood and Plasma Bank

TRANSFUSION REACTION NOTES

Blood .....cc. Plasma.....cc.

Date of Administration.....

Patient's Name .....Ward.....

1. Time Transfusion Started.....
2. Time Transfusion Stopped.....
3. Amount Patient Received..... cc.
4. Time of Reaction .....
5. Length of Reaction.....
6. Reaction
   a. Chilling Sensation .....
   b. Frank Chill .....
   c. Length of Chill .....
   d. Urticaria .....
   e. T° Before Transfusion .....
   f. T° After Transfusion .....

(signed) .....
Nurse

DO NOT WRITE BELOW THIS LINE

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BLOOD BANK REPORT

Hemolytic Reaction .....

Major Pyrogenic Reaction.....

Minor Pyrogenic Reaction .....

Urticarial Reaction .....

Remarks: .....

.....

.....

(signed) .....

JOHN SEALY HOSPITAL

Infusion Reaction Notes

Solution Administered

..... cc.

Date of Administration .....

Patient's Name..... Ward.....

1. Time infusion started.....
2. Time infusion stopped.....
3. Amount patient received..... cc.
4. Time of reaction.....
5. Length of reaction.....
6. Reaction
   a. Chilling sensation .....
   b. Frank chill .....
   c. Length of chill .....
   d. Urticaria .....
   e. T° before infusion.....
   f. T° after infusion .....

(signed) .....
Nurse

DO NOT WRITE BELOW THIS LINE

- -

INFUSION REPORT

Hemolytic Reaction .....

Major Pyrogenic Reaction .....

Minor Pyrogenic Reaction .....

Urticarial Reaction .....

Remarks: .....

.....

.....

(signed) .....

Cleaning and Preparation of Equipment

The installation of a sterile equipment and solutions room has aided us greatly in reducing our pyrogenic reactions. This room is clean and as near "dust-free" as possible. A single still assures us of constant "pyrogen-free" water. The walls are equipped with clean shelves which contain all of the intravenous solutions used in the hospital. The shelves are clearly labeled with kind of solution and amount and are kept orderly at all times. There is a combination work table and cabinet which has various compartments and drawers for holding equipment. The whole top of this cabinet lifts up and forms a work table on which the equipment is assembled. An autoclave is near where all equipment is sterilized and marked. A large sink for washing equipment is necessary.

It is wise for the majority of hospital blood banks to purchase their equipment and intravenous solutions from a reputable company. Always, the administration and withdrawal of blood should be a closed system. The initial expense of purchasing this equipment is offset by the following advantages:

1. Security in knowing the bottles are sterile and the solutions are pyrogen-free.
2. Technical problems are answered promptly by these companies. In instances where technique may be involved, a technical expert is sent to the individual hospital for consultation.
3. The hospital that prepares its own solution and bottles will find that the salaries paid the necessary personnel is almost equal to the expense of purchasing equipment.
4. The reaction rate in any hospital will drop considerably if commercially prepared solutions are used.

Cleaning Procedures

It is the responsibility of any blood bank or transfusion service to render their equipment as pyrogen-free as possible. There is no excuse for any hospital to overlook any of the finer points in cleaning procedures with the ultimate result of an elevated "pyrogenic-reaction" rate. Institutions are justly proud of a

minimum reaction rate as this record shows the results of scrupulous and painstaking care in the cleaning and assembling of equipment.

All metal parts, steel mesh filters, all rubber equipment, all glassware and all needles are cleaned with the following technique:

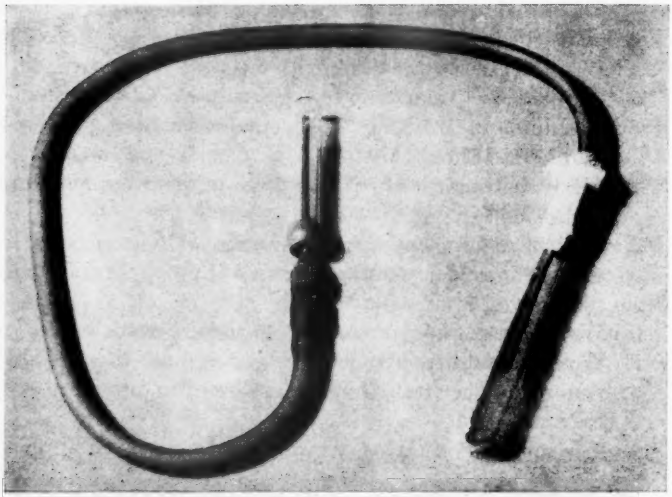
1. Wash all parts in liquid soap. Rubber tubing and glassware are cleaned with brushes. Needles are cleaned with stylettes.
2. Wash all parts three times with tap water to remove soap.
3. All parts are immersed in 4% sodium hydroxide for a minimum of 12 hours. The container used is a covered stainless steel pan.
4. Wash well in tap water three times to remove the sodium hydroxide.
5. Soak all equipment for a minimum of five minutes in 3% acetic acid to neutralize any sodium hydroxide possibly left on equipment.
6. Wash in tap water three times to remove acetic acid.
7. Wash in distilled pyrogen-free water three times. This water must be fresh from the still and in no event over four hours old.
8. The sets are assembled, wrapped and autoclaved at once.

All equipment, including rubber tubing is put through the above cleaning procedure after each time it is used. These stringent procedures may necessitate the replacement of rubber tubing more frequently but has proven worthwhile.

The Donor Set

We have found that it is unnecessary to use any valves in connection with our withdrawal of blood from donors. Instead, a very compact and facile set is prepared from a 16-inch piece of pyrogen-free rubber tubing, 5/32 of an inch in diameter. In each end of the rubber tubing is placed a 16 gauge stainless steel needle and adapter. We have found that this gauge is preferable for our use. One needle is protected by a small vial with a rubber stopper. This needle is placed in the rubber

diaphragm on the bottle. The needle which is used to penetrate the donor's arm is protected by an ordinary test tube with a cotton stopper. The rubber tubing is transparent and the flow of blood is easily observed. The rate of flow is easily regulated by finger pressure. This set is advantageous as far as assembling, cleaning and venipuncture procedures are concerned.

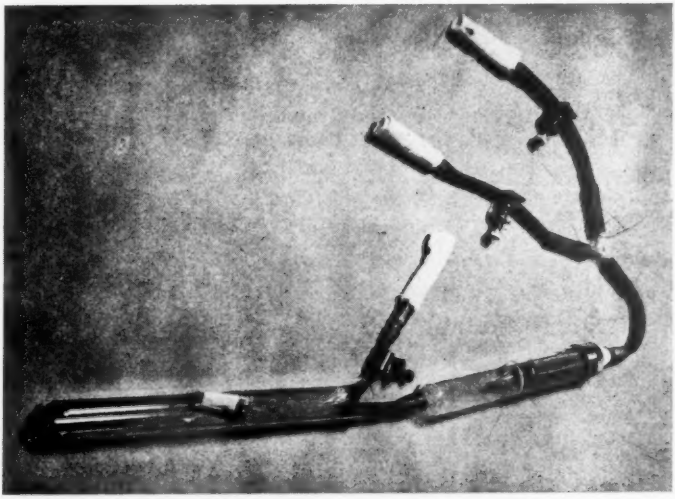


Donor set showing the cotton stoppered 16-gauge needle for venipuncture and the 16-gauge needle for bottle penetration.

The Recipient Set

We have adopted cellophane tubing throughout our hospital in regard to all intravenous therapy—that is, the administration of both intravenous fluids and blood. Our technique for cellophane tubing has been established from the article by Levinson, Wolf and Naftulin (1944). Our procedure for assembling our equipment is similar to that outlined by this paper except that we do not test our cellophane tubing for "pinhole" leaks. It is not practical for us to do this as we have found that is extremely rare to have a leak occur in this heavy

walled viscose tubing. This procedure consumes a great deal of time and the advantages are few. We also feel that filling the tubing with air may force foreign material into the tubing and thus possibly cause pyrogenic reactions.



Recipient set showing complete assembly of parts. The bottle adapters and the needle adapter are covered with unbleached muslin to prevent contamination during the unwrapping of the set.

Treatment of the Donor

The treatment given a donor is an important item in the operation of a blood bank. If the donor is treated kindly and with understanding he will be more than willing to come again and will assure his family and friends of the safety connected with blood donations.

The technician must not develop a routine as every donor is an individual and must be treated as such. Polite and sincere inquiries as to the donor's work, family, interests, etc., should be made by the technician. This aids greatly in reassuring the

layman and often prevents syncope. In any event, the technician must refrain from referring to the patient's condition for whom the donor is contributing blood.

The procedure prior to venipuncture is extremely minute in detail. The donor is questioned as to our rules and regulations. If the oral questioning is satisfactory, his temperature and hemoglobin are taken. If normal, a complete card is filled out.

☐ Charted

DONOR'S CARD
JOHN SEALY HOSPITAL
BLOOD AND PLASMA BANK

Race .....
Date .....

Donor's Name.....Age ..... Blood No.....

Address ..... Weight.....

Phone ..... Sex.....

Deposited to..... Rh Factor .....

PHYSICAL HISTORY

Blood Group .....

☐ Malaria
☐ Asthma
☐ Hay Fever
☐ Urticaria
☐ Recent Illness
☐ Recent Infection
☐ Tuberculosis
☐ Heart Condition

Serology .....

Whole Blood .....cc.

Packed Cells .....cc.

Temperature.....Degrees

Hemoglobin..... per cent

Converted into Plasma (Date) .....Lot No.....

The donor is placed on the donor bed in a recumbent position and his card is placed under the transfuso-vac on the bedside table.

1. The first procedure regarding venipuncture is to place the sphygmomanometer on the upper arm. The pressure is raised to 80 mm. of mercury. Higher pressure will result in cutting off the circulation and the vein will collapse soon.
2. The vein is palpated in the ante-cubital fossa to determine the site of needle penetration.

3. The arm is sponged off with tincture of mercresin and followed by alcohol.
4. One-half cc. of 1% novocaine with suprarenin is injected approximately ½ inch below the predetermined site of venipuncture to one side of the vein.
5. The donor is given a small rubber bulb to squeeze in his hand during the procedure.
6. The top of the transfuso-vac is uncovered but the small cellophane cap is left on until the needle is ready to puncture the cap. This insures sterility of the rubber stopper.
7. The donor set is unwrapped and the cover is used to conceal the transfuso-vac. This is done to prevent the donor from seeing the actual flow of blood.
8. The needle is introduced into the donor's arm in one motion and then injected into the vein. The rubber tubing is transparent and the blood shows clearly in the tubing when the vein is penetrated. The tubing is clamped off by using finger pressure.
9. The needle tube covering the other needle is removed and plunged through the "x" on the top of the transfuso-vac stopper.
10. The finger pressure on the tubing is released and the blood is allowed to flow into the bottle. The flow is regulated by finger pressure throughout the procedure. The donor alternately opens and closes his hand on the small rubber bulb.
11. When 500 cc. of blood have been obtained, the pressure is released in the sphygmomanometer and the bottle needle is withdrawn. This needle is placed in a pilot tube attached to each transfuso-vac by means of adhesive tape. This tube is used for typing, serology and compatibility tests.
12. The needle is then removed from the vein and an alcohol sponge is placed over the wound. The technician applies pressure immediately over the wound, placing three fingers along the vein. This is done to prevent any slight

exudation of blood from the vein and thus prevents the formation of any hematoma.

13. A pressure bandage is applied using a clean alcohol sponge and two-inch gauze bandage. The donor is requested to keep this bandage on for at least three hours.
14. The donor is allowed to rest for ten minutes and dismissed if there is no evidence of any syncopal reaction. Coffee is given to those donors who request it. We have found that cold or hot drinks served immediately after the donor has given blood will often cause nausea and vomiting. Furthermore, threatened syncope can sometimes be avoided by giving the donor a piece of lump sugar immediately prior to his donation.

Care of the Blood After Withdrawal

1. Immediately after the withdrawal of blood, the transfuso-vac and donor's card are removed to the laboratory.
2. Each bottle is given the number on the withdrawal card. This number is marked on the transfuso-vac, the donor's card and the pilot tube. The pilot tube is removed and placed in a test tube rack for subsequent typing, serology and compatibility tests. The withdrawal card is placed on the transfuso-vac and then placed on a special rack in the icebox until the necessary tests have been done. Labeling correctly is an absolute essential. The numerical system eliminates the possibility of nominal mistakes.

Blood Grouping

1. A 2% cell suspension in normal saline is prepared by gently rimming the clot with a wooden applicator and then agitating the applicator in the saline.
2. Clean glass slides are essential in every procedure. Glass dropping pipettes with rubber suction bulbs are used. These are washed six times with tap water and then six times with normal saline before each test.
3. Two circles are drawn on the slide with a china marking pencil. The number of the donor is placed on the right

end of the slide. One drop of the unknown cell suspension is placed in each circle. One drop of known "A" typing serum is placed in the left hand circle, and one drop of known "B" typing serum is placed on the right hand circle. Separate tooth picks are used to mix the cells with the typing serum.

4. The slide is allowed to stand for a minimum period of five to ten minutes and then read microscopically. The results are recorded on the card and on the bottle. Commercial blood grouping serum is used as this assures us of potent serum with a minimum of error.

Serology Tests

1. The clot is centrifuged and the serum is withdrawn for a serology test. The test employed will be determined by the serology test accepted in the State.
2. If the serology test is negative, the serum and clot are attached to the bottle, the cards are all properly marked "Serology Negative" and the bottle placed in the active blood bank until used. No blood is used after seven days and all serology positive blood is immediately discarded.

DONATION NO.....

Race.....

Date Withdrawn .....Time.....A.M. P.M.

Blood Group ..... Rh Factor.....

Serology .....

.....
Technician's Signature

Procedure Regarding Patient

It is the doctor's responsibility to try to secure donors for his patient. The nurses and attending physicians are also very coöperative in this matter. Each patient has an accurate record kept regarding his "debits" and "credits." These cards are

filed by the "Kardex" system to assure rapid location. The cards are permanent and show the patient's name, ward, service and blood group. One side of the card is for debits and one side for credits. The credit side shows the donor's name, date and amount contributed to the patient. The debit side shows the date, donor's number and amount received by the patient.

Procedures Regarding Transfusions

1. When the attending physician orders a transfusion on a patient, 5cc. of clotted blood is drawn from the patient. The tube and requisition card are labeled carefully. The blood sample and the requisition card are sent to the blood bank. No sample is accepted unless it is completely labeled.

☐ Charted RECIPIENT'S CARD Race .....

JOHN SEALY HOSPITAL

BLOOD AND PLASMA BANK

Patient's Name .....Date .....Service.....

Diagnosis .....Ward.....Age.....Sex.....

Please check:

☐ Whole Blood ..... cc.
☐ Plasma ..... cc.
☐ Packed Red Blood Cells..... cc.

☐ Emergency .....
☐ To Be Transfused (Date).....
☐ For Operation on (Date).....

Signed .....
Attending Physician

LABORATORY DATA

RH Factor .....

Blood Group .....

Compatible with .....

.....
Technician's Sig.

2. The sample is grouped, and blood of the same group is selected. If we do not have the patient's blood group in the bank, a group "O" or "universal donor" is used. We have used a tremendous number of universal donors to date and have had no untoward reactions from this

procedure. We deem it a safe measure to employ and it is certainly advantageous for the small blood bank.

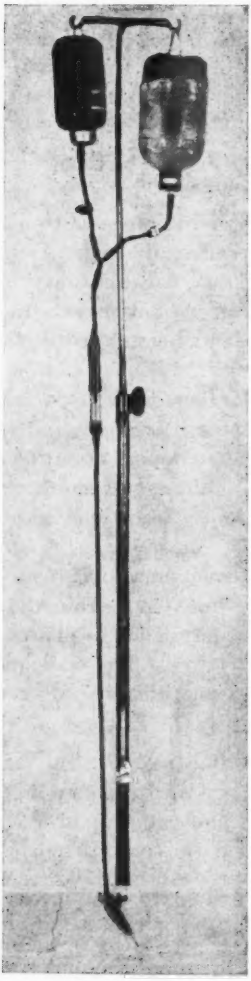
3. The donor's card is stapled to the recipient's card. In every instance of blood transfusion it is necessary that a compatibility or cross-matching test be performed. This is done to make certain that the patient's serum contains no iso-agglutinins which will hemolyze or agglutinate the red blood cells of the donor.

In certain patients receiving repeated transfusions irregular iso-agglutinins may appear in the patient's serum as a result of iso-immunization. Thus, it is necessary for the blood bank to require a recompatibility test after each transfusion to eliminate the possibility of a fatal hemolytic reaction as recommended by Wiener and Peters (1940).

Compatibilities on infants must be done as at birth the serum of the infant may contain iso-agglutinins of maternal origin, so that the use of random donors might be dangerous according to Wiener (1941). Infants receiving repeated transfusions must have recompatibility tests done because of the same reasons stated above.

In case of severe emergency, when no time can be spared for the compatibility test, blood from the blood bank will be given out only if the physician in charge of the patient will sign a compatibility waiver. The compatibility waivers serve only to show the extreme measures deemed necessary by the physician.

4. A major compatibility test, using Vincent's slide method, is done for every transfusion by mixing one drop of the patient's serum and one drop of a 2% cell suspension of the donor's red blood cells. The slide is covered with a Petri dish to prevent evaporation for a period of 20 minutes.
5. At the end of 20 minutes, the slide is read microscopically. If there is no clumping, the donor's blood is compatible with the patient's blood. If there is clumping, the transfusion is deemed unsafe and a new donor is selected. If it is still incompatible, the patient's serum is tested with



Recipient set showing the actual suspension of blood and solution for administration.

each bottle of the same group in the bank at room temperature, ice-box temperature (4°C.) and at incubator temperature (37°C.). If there is no clumping at 37°C., but it is clumped at 4°C., the reaction is due to cold agglutinins and the blood can be administered. If it is due to cold agglutinins, the compatibility tests at ice-box temperature will be strongly clumped. Rouleaux formation is no contraindication to blood transfusions.

If clumping occurs at all temperatures, the transfusion is cancelled and another sample is requested on the following day. Atypical agglutinins appear to be very transient and repeated samples are requested until a compatible donor is secured.

6. When the test is compatible, the card and the bottle are marked "compatible" and the blood is placed in the bank to be called for by the ward maid. The bottle is accompanied by a sterile administration set.

The Administration of Blood

When the blood arrives on the ward, the nurse notifies the doctor and sets up the bedside table. The patient's temperature, pulse and respirations are recorded prior to the transfusion. The doctor unwraps the set carefully.

Directions for Using the Transfusion Equipment

1. The doctor removes the cellophane tubing from the large test tube and the paper band from the tubing. The large test tube is filled ¾ full with tap water and the cellophane tubing is immersed in this water for at least one minute.
2. The rubber disc is cut from the top of the bottle and the top is sponged off with an alcohol sponge. All clamps on the set are closed.
3. A sterile needle is plunged into the small indentation as an air inlet.
4. The connecting tube adapter is plunged through the larger opening. This procedure is facilitated by previously puncturing this indentation with some sterile instrument.

5. The bottle is rotated gently and suspended on a standard. All clamps on the set are opened.
6. The blood or solution is allowed to enter the tubing until it reaches the needle. The clamps are again closed.
7. The tourniquet is placed on the patient's arm. The antecubital fossa is sponged off with dilute iodine followed by alcohol.
8. The needle is inserted into the vein, the tourniquet is removed, and the clamps are opened. The doctor regulates the flow (15 drops approximates 1 cc.) by adjusting the clamps.
9. In using intravenous solutions in combination with the blood, the set is first filled with the solution. The fluids and the blood can be given separately or simultaneously by merely adjusting the clamps.
10. When the transfusion is completed, discard the cellophane tubing and wash all parts of the equipment in tap water. The equipment is sent to the sterile equipment room for cleaning.
11. The nurse records the patient's temperature, pulse and respiration following the transfusion. Any untoward reaction in the patient is recorded on a Reaction Report and this is reported to the blood bank for investigation. The withdrawal slip on the bottle is attached as a permanent record to the patient's chart.

WITHDRAWAL SLIP

.....Whole Blood

.....Red Cells Race.....

.....Plasma

Recipient .....Ward.....Service.....

Group .....Rh Factor.....

This Blood is Compatiable with:

Donation Number ..... Group..... Rh Factor.....

Date ..... Time..... A.M. P.M.

.....

Technician's Signature

To Be Charted

Conclusion

This paper has not dealt in any way with plasma preparation, packed red blood cell transfusions or with the Rh factor. It has been written primarily to aid the average hospital in the initial institution of a transfusion service.

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SULFASUXIDINE AND SULFATHALIDINE*

EDGAR J. POTH

On a visit to Johns Hopkins in the Spring of 1940, Doctor W. M. Firor told me that a substance had been found which would sterilize the gastrointestinal tract. The substance was sulfanilylguanidine, synthesized by Roblin, Williams, Winnek, and English (1940), and studied by Marshall and his coworkers who claimed the compound to be poorly absorbed from the bowel. These claims, if true, were of great significance because they marked a milestone in surgery involving the gastrointestinal tract.

Returning to the staff of the Johns Hopkins University School of Medicine in July 1940, I began the study of the effect of sulfaguanidine on the gastrointestinal tract, first on the dog and then on man. These studies revealed that this drug does not alter the coliform organisms of the gastrointestinal tract significantly when ulcerations are present, and that it is extensively absorbed from the bowel of both dog and man. Dogs given large doses of sulfaguanidine all developed stones of crystalline, unaltered drug to fill the kidney pelvis completely. When the drug is administered in full therapeutic doses to man, approximately 50% of the sulfonamide is excreted in the urine. Furthermore, it was observed that approximately 25% of individuals receiving sulfaguanidine at 4 hour intervals exhibited untoward drug reactions of sufficient severity to require discontinuance of the therapeutic measure. Because of the severity of reactions and the lack of evidence that the drug consistently caused a significant alteration of the bacterial flora of the gastrointestinal tract, the administration of sulfaguanidine as a preoperative measure in preparation for surgery on the colon was discontinued in the Department of Surgery at Hopkins before any other drug had been found to replace it (Table I).

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*From the Departments of Surgery and the Surgical Research Laboratory of The University of Texas Medical Branch, Galveston, Texas. Received for publication January 22, 1946.

TABLE 1

A Comparison Between Phthalylsulfathiazole, Succinylsulfathiazole and Sulfanilylquanidine When Administered Orally to the Dog.

Drug	Dose gm/kilo/ day	Drug Conc. in Blood Mgm. per 100 cc.		Drug Conc. in Urine Mgm. per 100 cc.		Relative Bacterio-stasis
		Free	Con-jugated	Free	Con-jugated	
Phthalylsulfathiazole	1.0	3.0	3.0	.....	.....	++++
Succinylsulfathiazole	1.0	3.5	5.0	360	600	++++
Sulfanilylquanidine	1.0	15.0	.....	Crystals	.....	++
Phthalylsulfathiazole	0.5	2.3	2.7	174	210	++++
Succinylsulfathiazole	0.5	3.5	4.0	180	600	+++
Sulfanilylquanidine	0.5	11.0	.....	Crystals	.....	++
Phthalylsulfathiazole	0.25	1.5	2.4	180	200	+++
Succinylsulfathiazole	0.25	4.0	4.0	125	560	++
Sulfanilylquanidine	0.25	7.0	.....	1,960	.....	+ —

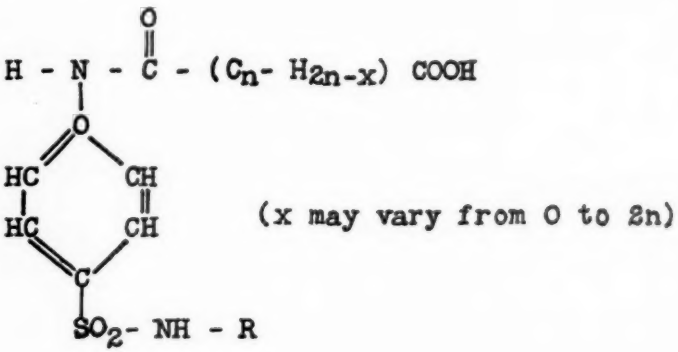
In the Fall of 1940, I outlined a plan by which it was hoped that a compound could be found which would possess the properties of an intestinal antiseptic. Ideally such a compound should be poorly absorbed from the gastrointestinal tract, non-irritating to the bowel, non-toxic, possessed of antibacterial activity, and maintained in the lumen of the bowel in high concentration. At that time, some 1200 sulfonamides had been synthesized, of which, only a few had been shown to be both non-toxic and possessed of antibacterial activity of therapeutic value. The ordinary procedure for demonstrating bacteriostatic activity was to administer the compound orally to mice which were then, or had been, inoculated intraperitoneally with streptococci or pneumococci and the survival rate observed. If the animals were not protected, the drug was considered as having insignificant therapeutic properties and was discarded without studies being made to determine whether or not the drug was absorbed from the gastrointestinal tract. Thus a compound not absorbed from the gastrointestinal tract would fail to protect the test animal even though the compound possessed strong antibacterial activity. From these considerations, the following plan of procedure was outlined. First, the dog was chosen as the test subject, because the normal bacterial inhabitants of the gastrointestinal tract of this animal resembles

those of man. Second, the compounds to be studied would be those which had been synthesized by various manufacturers but discarded because no bacteriostatic activity had been demonstrated by the usual plan of investigation. Third, these sulfonamides would be administered at 4 hour intervals, and the bacterial flora of the gastrointestinal canal observed.

Escherichia coli is a normal inhabitant of the gastrointestinal tract of the dog, it is moderately resistant to the antibacterial action of the sulfonamides, and the cultural characteristics of this bacterium are such that it can be followed quantitatively quite simply. It was, therefore, planned to follow the population of the coliform organisms during the period of preliminary observation. Should a compound give evidence of antibacterial activity as reflected by alteration of the coliform flora, then more exhaustive studies including the investigation of absorption, excretion, acute and chronic toxicity, the antibacterial activity against organisms other than the coliform bacteria, and the histological studies of specimens obtained at autopsy would be carried out on the dog and other laboratory animals. Should a poorly absorbed, non-toxic drug, possessing bacteriostatic properties be found, it would then be administered to normal human volunteers for further studies.

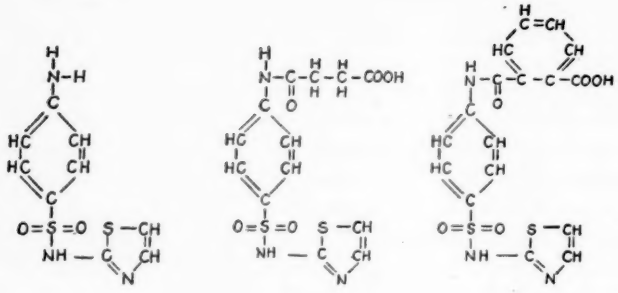
Doctor W. A. Feirer, then Medical Director of Sharp and Dohme of Philadelphia, was among the first to whom the above plan was presented. It was agreed that they would furnish compounds for study. A number of compounds were studied without success. One day Doctor M. L. Moore, also of Sharp and Dohme, told me that they had made succinylsulfanilamide and asked if we should wish to test it. We did. Succinylsulfanilamide was not a new compound. It had been synthesized previously and is described in British patent 502,558 (March 15, 1939). There was only meager hope that it would possess antibacterial properties. It had failed to protect mice against the lethal effect of the intraperitoneal injection of streptococci according to Moore, Miller, and Miller (J. Am. Chem. Soc. 62, 2097–99, Aug. 1940). On April 12, 1940, Perrin H. Long reported to E. H. Northey that the sodium salt of succinylsulfanilamide possessed no bacteriostatic activity.

Succinylsulfanilamide effected a significant alteration of the coliform flora in the bowel of the dog and became the first member of a long series of sulfonamides studied. This series is characterized by the fact that the primary, para-amino group of the sulfonamide is acylated using a dicarboxylic acid. The general formula for this series of amic acids is represented as follows:



An extensive program was then undertaken to synthesize compounds corresponding to various possible combinations of the dicarboxylic acids, oxylic, maleic, succinic, malonic, quinolinic and phthalic, and the sulfonamides, sulfanilamide, sulfathiazole, sulfapyridine, sulfadiazine, sulfamethyldiazine, sulfanilylguanidine, sulfanilhydroxamide, sulfanilylsulfanilamide, sulfanilylsulfathiazole, and sulfanilamidoethylthiazolidone, in a search for those compounds of greatest promise of therapeutic value. This search resulted in the discovery of several substances which possessed antibacterial properties, were poorly absorbed from the gastrointestinal tract, and were non-toxic in therapeutic doses. The two most promising of these are succinylsulfathiazole (sulfasuxidine) and phthalylsulfathiazole (sulfathalidine) (Figure 1).

These two compounds were studied exhaustively on various laboratory animals to determine their bacteriostatic activity and toxicity. Sulfathalidine was found to be two to four times as



Sulfathiazole *Succinylsulfathiazole* *Phthalylsulfathiazole*
"*Sulfasuxidine*" "*Sulfathalidine*"

Figure 1. This chart shows the structural formulae and interrelationship chemically of the acylated sulfonamides, sulfasuxidine and sulfathalidine.

effective as sulfasuxidine in causing a reduction of the coliform organisms in the gastrointestinal tract. Approximately 5% of the ingested dose of either drug is excreted in the urine. The toxicity of both is practically the same at equal dosage levels. The extensive studies on experimental animals will not be recounted, but the preliminary studies on man, and the subsequent therapeutic uses of these two drugs will be reviewed in some detail.

Sulfasuxidine was first described by Poth and Knotts (1941) as an intestinal antiseptic, and sulfathalidine was introduced in 1943 by Poth and Ross. Subsequently these drugs have been studied by many investigators and their use has been extended and rather firmly established as intestinal and urinary bladder antiseptics. The antibacterial action of these compounds effects a considerable reduction of the gram negative flora of the bowel: both anaerobic and aerobic organisms being susceptible (Figures 2 and 3).

As an indicator of such effect the alteration of the coliform organisms is followed. These organisms are well adapted to this purpose, because they are moderately resistant to the anti-

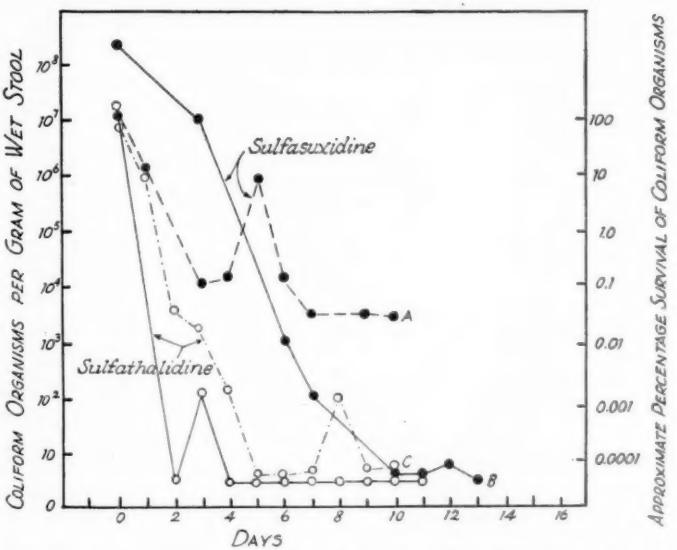


Figure 2. A comparison of the relative bacteriostatic activity of sulfasuxidine and sulfathalidine as indicated by the alteration of the coliform flora in the gastrointestinal tract of man when various doses of the drugs are administered orally at four-hour intervals. *A* represents the results following a daily dosage of 0.125 gm. of succinylsulfathiazole per kilogram of body weight; *B*, following a daily dosage of 0.25 gm. of succinylsulfathiazole; *C*, following a daily dosage of 0.125 gm. of phthalysulfathiazole; and *D*, following a daily dosage of 0.25 gm. of phthalylsulfathiazole.

Compare *A* with *C*, and *B* with *D*.

0.25 gm. per kilo is the recommended daily therapeutic dose for sulfasuxidine while for sulfathalidine, the corresponding dosage is 0.125 gms.

bacterial action of sulfonamides, and their cultural characteristics are such that they can be estimated by simple techniques using desoxycholate or eosin-methylene blue media. A simple technique sufficiently accurate for the practical demonstration of a clinically significant alteration of the coliform flora consists of mixing a small portion of feces with a drop of 5 mg. per cent para-aminobenzoic acid solution on a sterile glass slide and then a desoxycholate or eosinmethylene blue agar plate is streaked with a 2 mm. loopful of this triturate thereby transferring and culturing approximately 0.01 Gm of feces. The number of

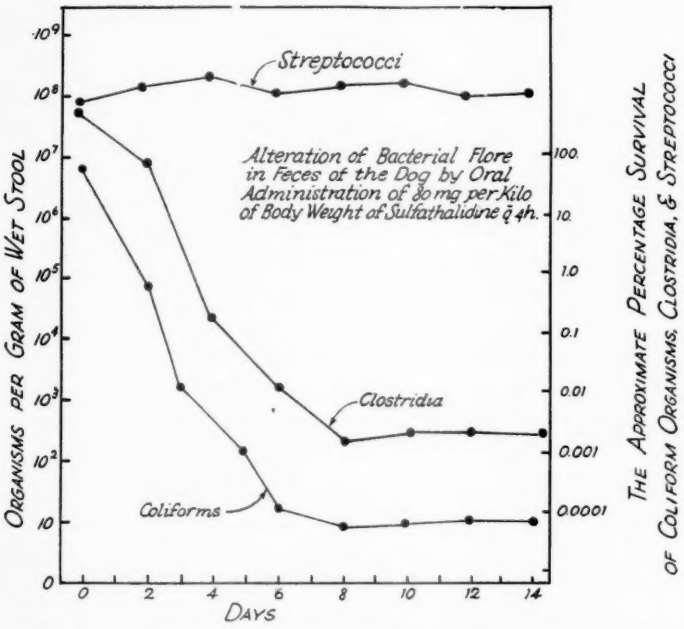

Streptococci
Alteration of Bacterial Flore in Feces of the Dog by Oral Administration of 80 mg per Kilo of Body Weight of Sulfathalidine q 4h.
Clostridia
Coliforms
Organisms per Gram of Wet Stool
Days
The Approximate Percentage Survival of Coliform Organisms, Clostridia, & Streptococci

Figure 3. This chart illustrates the antibacterial activity of sulfathalidine on three important groups of organisms. Essentially the same change is effected by sulfasuxidine when 160 mg. per kilo of body weight is given. The clostridia which remain are composed almost entirely of the spore forms.

colonies growing on such a preparation multiplied by 100 gives a rough estimate of the number of coliform organisms per gram of feces (Figure 4). When the coliform count has dropped to 1000, the coliform flora has been reduced 99.9 per cent, and this change is taken to indicate that the intestinal flora has been altered significantly.

If the alteration of the coliform flora is not followed, the drugs should be administered for a week for assurance of maximum effect preoperatively (Figure 5).

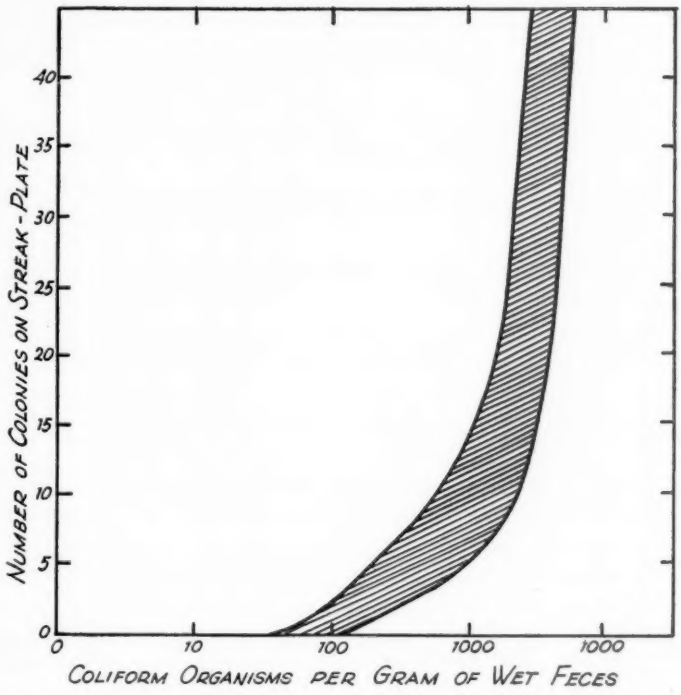


Figure 4. The use of platinum loop which will transfer approximately 0.01 gm. of fecal matter to streak a desoxycholate agar plate is sufficiently accurate to indicate when the bacterial flora has been significantly altered. Example: When the coliform count has been reduced to one thousand, the colony count on the streaked plate will vary from five to fifteen. (E. J. Poth, J. A. M. A., 120:265–268 (1942).)

Toxicity.—The sulfonamides are potentially dangerous drugs, and they must be given cautiously and under close supervision. Sulfasuxidine and sulfathalidine are relatively non-toxic. These drugs have been administered to several thousand individuals during the past five years. There is one recorded instance of a fatal acute agranulocytosis following the administration of 159 grams of sulfasuxidine in the course of 12 days to a patient known to be sensitive to sulfathiazole. It is not unusual to

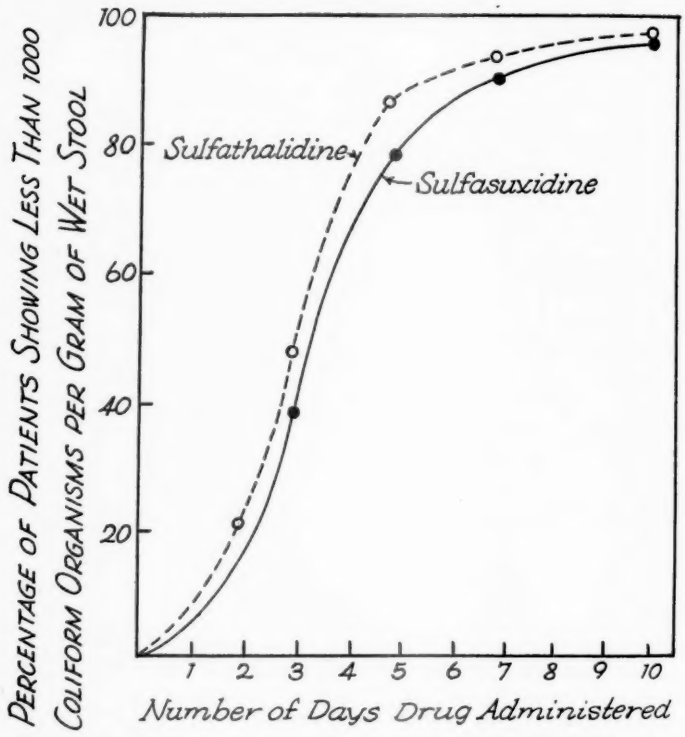


Figure 5. A diagrammatic analysis of the data on the alteration of the coliform organisms following the oral administration of full therapeutic doses of sudfasuxidine and sulfathalidine at four-hour intervals during the period of preoperative preparation of patients requiring colonic surgery.

encounter a moderate increase of temperature, anorexia, malaise, and headache. These mild symptoms do not require interruption of the therapy. Occasionally a rash may develop whereupon the medication should be discontinued. Of the two drugs, sulfathalidine is probably the least toxic at therapeutic dosage levels. Bargen reported toxic reactions of sufficient severity to indicate discontinuance of sulfasuxidine in 1 per cent of 2000 cases. Sulfathalidine was then given to these

patients sensitive to sulfasuxidine without the reappearance of toxic symptoms in a single instance.

Arthur W. Allen (personal communication) finds increased bleeding to occur in one-fifth of patients having a carcinoma of the colon after four to five days of sulfasuxidine administration. He does not observe increased bleeding after the administration of sulfathalidine. I have noticed an increased amount of bleeding in a few instances, but it has not been sufficient to cause a change in the preoperative management or to force an emergency operation. During the postoperative period there has not been a tendency towards increased bleeding. The bleeding time, clotting time, clot retraction, and prothrombin time have not been altered by the administration of either sulfasuxidine or sulfathalidine.

Dosage.—These drugs which are sparingly absorbed have their action limited largely to the gastrointestinal tract. The amount of drug required to alter the intestinal flora will be determined by the contents of the bowel, its mucosal surface area, and the rate at which the drug passes over this surface rather than by the weight of the patient. The effective dose of sulfasuxidine is 3.0 grams every four hours for an average sized adult. Since sulfathalidine has twice the bacteriostatic activity of sulfasuxidine, its dose is one-half as much or 1.5 grams every four hours. In the presence of an extensive diarrhea, the dosage must be doubled. Sulfathalidine is the drug of choice when diarrhea is present or whenever purgatives and enemas are used. Symptoms of acute toxicity can not be brought on with massive oral doses of these drugs.

The Indications for Sulfasuxidine and Sulfathalidine Administration

These sparingly absorbed sulfonamides have various uses. They are indicated in the preoperative preparation of both the small and large bowel, and in the treatment of chronic Escherichia coli infections of the urinary tract, of both acute and chronic bacillary dysentery, of the diarrheas, of regional enteritis, and of chronic ulcerative colitis.

The Preoperative Preparation of the Bowel

The preparation of the gastrointestinal tract for operation demands first that the bowel be empty of fecal material and gas. Formerly purgation, enemas, and a starvation diet were used to accomplish this condition and resulted in a dehydrated, semi-starved patient. The bowel can be rendered free of gas and fecal material by giving a low residue diet, rich in proteins with adequate carbohydrates and fat by simultaneous administration of sulfasuxidine. Malnutrition is often present in patients suffering with lesions of the gastrointestinal tract due to long restriction of diet. Many of these patients have anorexia due to avitaminosis, hypoproteinemia, edema of the mucous membrane of the bowel, and fatty infiltration of the liver. Three or four days administration of amino acids and vitamins intravenously will restore the patient's appetite to take an adequate diet. It is imperative that the avitaminosis, the hypoproteinemia and the fatty infiltration of the liver be corrected prior to an operation. Hypoproteinemia results in excessive edema at the line of suture, and patients with fatty livers tolerate anesthesia poorly. Only the simplest emergency operations should be undertaken when the A–G ratio is abnormal and the plasma protein concentration is less than 5.5 per cent. In the absence of obstruction, the patient is placed on a residue-free diet high in carbohydrates and protein. Strained fruit juices fortified with lactose, casein, jello, gelatin and partially hydrolyzed proteins such as "Essenamine" should be given in sufficient quantities to provide a minimum of 2 grams of protein per kilo of body weight and 3000 calories daily. Simple carbonated drinks aid the patient in taking the diet. Patients accustomed to alcoholic beverages usually tolerate them well and have improved appetites when such drinks are allowed in moderate quantities. An adequate diet can be taken while sulfasuxidine is administered to empty the bowel mechanically and lower the bacterial flora significantly.

Preoperative Preparation by Sulfasuxidine

The coliform bacteria in the feces is reduced to less than 1000 organisms per gram of wet stool when 3.0 grams of sulfa-

suxidine is given by mouth every four hours to adults in the following times: (1) 37 per cent within 3 days of therapy, (2) 80 per cent within five days, and (3) 94 per cent within seven days. If the alteration of the coliform flora is followed by the "streak technique," the preoperative administration is continued until the colonies of coliform organisms are less than twenty. If no observations are made on bacterial counts, the drug is administered for seven days to ensure optimum bacterial alteration. In any event, the patient must have had at least one bowel movement daily. The stool ordinarily becomes semi-fluid, small in bulk and relatively odorless. Should a watery diarrhea develop, sulfathalidine in equal dosage should be substituted for the sulfasuxidine. Occasionally 1.5 grams of both drugs is given every four hours. It is not necessary that the entire dose be taken at one time, but, with a coöperative patient, the drug may be taken in broken portions throughout the four hour period. Should an enema be given on the evening preceding the operation, it should contain 10 grams of sodium bicarbonate and 6 grams of powdered sulfasuxidine or sulfathalidine per liter of sterile water. Sulfasuxidine administration usually results in three or four small bowel movements daily, and an enema is not needed to give an empty, collapsed bowel at the time of operation.

Preoperative Preparation by Sulfathalidine

The procedure for the preparation is essentially the same for sulfathalidine as it is for sulfasuxidine. The dosage of sulfathalidine is 1.5 grams every four hours. There is less tendency for the stools to become semi-fluid, and more attention must be directed towards ensuring an empty bowel when sulfathalidine is given, because the feces becomes rather tenacious and stringy with a tendency to adhere to the bowel wall. The patient must have a bowel movement daily with a progressively decreasing bulkiness even if a mild cathartic must be administered. Should a watery diarrhea be present, the dose should be increased to 3.0 grams every four hours. Enemas should again contain bicarbonate and sulfathalidine.

The sulfonamides are bacteriostatic substances, and so the drug must come in contact with the entire mucosal surface if a significant alteration of the bacterial flora is to be realized. If a fecal fistula or enterostomy diverts the drug away from a distal segment of bowel, then an equal quantity of drug must be introduced into such a distal segment. In the presence of diverticulae, the time required to alter the flora is prolonged.

My preference for sulfasuxidine is not shared by all surgeons using these two drugs. Whether sulfasuxidine or sulfathalidine is superior will be determined by the entire preoperative management. They should not be used in an identical manner. When purgatives and enemas are used, sulfathalidine will be superior to sulfasuxidine. After treating 2,075 patients with these drugs in 1943 and 1944 Bargen makes the following observation: "Succinylsulfathiazole (sulfasuxidine), so far, has proved to be the drug of choice in preoperative management, with phthalylsulfathiazole (sulfathalidine) serving as an alternative when toxicity to succinylsulfathiazole manifests itself."

Since only about 5 per cent of the ingested drugs are absorbed and the rate of excretion in the urine is rapid, the blood levels of the drugs need not be determined routinely. A patient need not be hospitalized during his entire period of preoperative preparation.

Administration Following Operation

Sulfathalidine should be given in full therapeutic doses until the twelfth postoperative day so as to control the intestinal flora beyond the period of possible leakage at the line of suture following primary anastomosis of bowel. Gastric suction is used for the first twenty-four hours postoperatively, because considerable quantities of air may be swallowed in this interval which includes recovery from anesthesia. Thereafter, the patient will tolerate cool water in 30 cc. quantities hourly and 1.5 grams of sulfathalidine every four hours. The drug is tolerated surprisingly well, especially if the 0.5 gram tablets are taken singly during the four hour interval.

These drugs are particularly indicated for the preoperative preparation and the postoperative control of the colon when the ureters are transplanted to empty into the rectosigmoid.

Sulfasuxidine and Sulfathalidine Therapy in Chronic Coliform Infections of Urinary Tract

It is not unusual to find cases of chronic E. coli infections of the urinary tract which will not respond to treatment with the ordinary antiseptics including the administration of sulfadiazine and sulfathiazole. In 1942 I saw such a case in an elderly lady. The urine contained 10^9 coliform organisms in each cubic centimeter. The stool contained 10^8, only 1/10 as many bacteria as the urine. Sulfasuxidine was given and the urine became sterile and the stool grew less than 10 coliform organisms per gram (Figure 6). It was felt that ridding the bowel of E. coli removed a constant source of reinfection of the urinary tract.

Subsequently, Everett published a considerable series of such cases which showed a high incidence of cures. Sulfathalidine is equally as effective.

Many of these patients complained of gaseous distention and chronic constipation which is alleviated simultaneously. Even though only 5 per cent of the ingested dose of the drugs is excreted in urine, the drugs form readily soluble salts and their ions are present in relatively high concentration.

Sulfasuxidine and Sulfathalidine Therapy in Bacillary Dysentery and Diarrheas

Poth, Chenoweth and Knotts (1942) described the treatment of acute bacillary dysentery using sulfasuxidine. Hardy, Burns, and DeCapito (1943) published a rather extensive report on the use of sulfasuxidine for this purpose. They found this drug the most useful in treating chronic cases and carriers especially of the resistant Sonne strains.

The treatment of diarrheas due to invasion of the gastrointestinal tract by various organisms not causing a recognized specific disease can not be attacked as directly, and the results

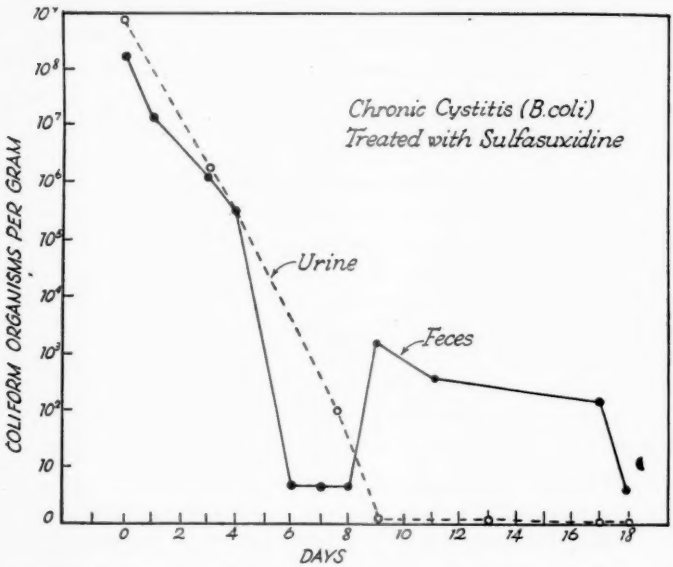


Figure 6. Demonstration of rapid disappearance of E. coli from the urine of a patient with a long-existing chronic cystitis. The urine became sterile between the third and ninth days. No coliform organisms present in the feces on the sixth day. The patient received 0.25 gm. of succinylsulfathiazole daily divided into six equal doses administered orally at four-hour intervals. (E. J. Poth and C. A. Ross, J. Lab. Clin. Med., 29:785–808 (1944).)

of treatment are less readily evaluated. Many diarrheas of unknown etiology do, however, respond favorably to treatment with sulfasuxidine and sulfathalidine. Sulfathalidine seems to be the drug of choice. On the other hand, the nonspecific diarrheas occurring in some regions are best treated with sulfapyridine. Always, special care must be directed towards preventing dehydration, especially in children and infants, when sulfapyridine is given.

Sulfasuxidine has been given in typhoid fever. There is no specific activity, since the sulfonamides are ineffective against the typhoid and paratyphoid organisms, but many of the troublesome gastroenteric symptoms are aleviated even though the disease otherwise runs an unaltered course. Should a

perforation of the ileum occur, however, the bacterial flora will have been altered and the dangers from a severe peritonitis lessened. Cultures taken from the peritoneal cavity of a patient who suffered such a typhoid perforation while taking sulfasuxidine failed to reveal the presence of coliform organisms.

Sulfasuxidine and Sulfathalidine Therapy in Regional Enteritis

These drugs are finding particular usefulness in the treatment of Crohn's disease. They are useful not only as a preoperative measure, but it is considered the course of choice in recurrences following either resection or short-circuiting operations. Of course, it is obvious that if they are beneficial for the treatment of recurrences, they will likewise be of value in the initial treatment of the disease. Their prolonged use should make surgical treatment unnecessary in many instances.

Sulfasuxidine and Sulfathalidine in the Treatment of Chronic Ulcerative Colitis

The successful management of this entity or symptom complex is of most interest to the Gastroenterologist, because little success has been achieved in the treatment of this condition. Of course, it is recognized that there may not be a single etiological factor and hence not a single cure. The lesions in the colon may be the mere obvious lesions of a more deeply seated disease or diseases.

The sulfonamides have come in for considerable study. While sulfasuxidine and sulfathalidine have not proved a ready cure, certain statements can be made regarding their value. Their use will frequently induce and maintain a remission. On occasion their effect is dramatic (Figure 7). The lesions visible by sigmoidoscopy will show but little change in less than one month's continuous treatment. My experience in the management of this condition indicates that the drugs must be administered continuously in full therapeutic doses for months. Obviously, individuals sensitive to the sulfonamides can not be candidates for treatment. Sulfathalidine is better tolerated and is the better drug in this instance. Anal fistulae may heal.

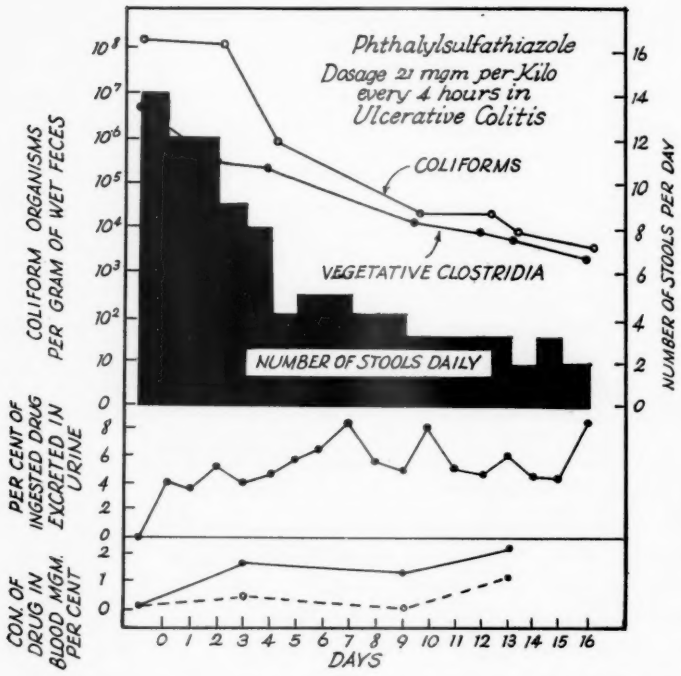

Phthalylsulfathiazole
Dosage 21 mgm per Kilo
every 4 hours in
Ulcerative Colitis
COLIFORMS
VEGETATIVE CLOSTRIDIA
NUMBER OF STOOLS DAILY
COLIFORM ORGANISMS PER GRAM OF WET FECES
NUMBER OF STOOLS PER DAY
PER CENT OF INGESTED DRUG EXCRETED IN URINE
CON. OF DRUG IN BLOOD MGM. PER CENT
DAYS

Figure 7. Illustration of the response of a severe case of ulcerative colitis of long standing to sulfathalidine therapy. The clinical response, with reduction of the number of movements and an increase of appetite, preceded a significant alteration of the bacterial flora of the bowel.

Even those patients who have suffered irreversible anatomical changes, and who must ultimately be treated by colectomy, are strikingly improved and become better candidates for operation with relatively normal plasma protein and protein reserves.

Discussion

The properties of sulfasuxidine and sulfathalidine have in their experimental and therapeutic application opened several intriguing fields of study. These compounds contain free a carboxyl radical which makes these chemicals strong acids when compared with other sulfonamides. Consequently, they

form salts readily which are fairly soluble and ionize extensively in aqueous solutions. This property eliminates crystalluria and one of the most serious untoward effects of sulfonamide administration.

It is surprising that these compounds, because of this same property are but sparingly absorbed from the bowel. Obviously, the poor absorption is not due entirely to the presence of a free carboxyl group, because the mere presence of this radical does not confer this characteristic on all sulfonamides or even on all acylated sulfathiazoles.

No discussion of these drugs would be complete without mentioning their "Mode of Action." Here our definitive knowledge is slight. We do know that these acylated compounds possess only weak, in vitro, bacteriostatic activity, and even this action might be due to contamination with the free sulfonamide or to free sulfonamide resulting from simple hydrolysis of the acylated compound. Why do these compounds show such unusual bacteriostatic activity locally in the gastrointestinal and urinary tracts? Is it because the soluble, highly ionized salts of these compounds maintain a high concentration of the active ions in the media of the bowel and the urine? If so, then they should show high in vitro activity, which is not the case.

It remains that the activity shown by these compounds must be linked with modifications of the drugs that occur in the gastrointestinal tract. These changes are probably not the simple hydrolysis of the acylated compounds to yield sulfathiazole, because, when sulfathiazole is given in large doses, the bacterial flora of the bowel is but slightly modified. When sulfathiazole is given in large doses, approximately 60 per cent is excreted in the urine leaving 40 per cent to be eliminated in the stools.

The following are a few of a number of possibilities which may explain the profound alterations of the bacterial flora of the alimentary tract induced by sulfasuxidine and sulfathalidine: 1) the action of the drugs per se and their anions determined by the physical and chemical properties of these com-

pounds and resulting in a high concentration of the compounds within the cells or upon the surface of an individual microorganism depending upon their specific absorption and adsorption; 2) the formation of nascent or excited substances in intimate contact with the individual microorganisms; 3) the formation of active products by the influence of a strain of organisms resistant to the drug or its split products but which products inhibit cell division of another accompanying strain or species of organisms; or 4) the effect of other possible products of hydrolysis such as succinic and phthalic acids. Succinate is an important substrate in certain oxidation-reduction chain reactions in respiratory enzyme systems and may exert its influence by being liberated in high concentration in intimate contact with individual microorganisms.

The ultimate substances responsible for the observed bacteriostatic activity of these compounds may result from the inhibition of the formation of essential substrates or by the formation of secondary inhibiting substances. The studies on nutrition which indicate alterations of bacterial synthesis of the vitamins of the B-complex, biotin and folic acid when rats are fed pure diets may be evidence pointing in the direction of an explanation of the "Mode of Action" of these compounds.

Regardless of the mechanism by which these drugs assert their bacteriostatic effect, it is well established that they alter profoundly the bacterial flora of the gastrointestinal tract, and their use for this purpose has had extensive trial and has led to the following statement by Pemberton: (Annals of Surgery, 121, 409, 1945) "The changes that have occurred in surgery of the colon since the introduction of chemotherapy have been as spectacular and revolutionary as the changes wrought by iodine therapy in surgery of exophthalmic goiter. The striking analogy has often occurred to me. Just as in the pre-iodine era of thyroid surgery the technical perfection of the surgical procedure of partial thyroidectomy was no definite assurance that the patient would endure the operation (for not infrequently a severe hyperthyroid crisis would supervene, resulting in death), so in the prechemotherapy era of colonic

surgery the technically errorless resection of a segment of intestine was not definite assurance that the patient would survive, for not infrequently infection would spread and produce fatal peritonitis. The surgeon in both fields, after resorting to refinement of technic and other measures, finally learned that the best means of combating the hidden danger (acute hyperthyroidism on the one hand and the spread of infection on the other) was to divide the operation into stages. In both fields the employment of the two-stage procedure resulted in great improvement but only partially eliminated the hidden danger peculiar to each. Thus, it was only after preoperative iodine therapy had been standardized that the surgeon could be reasonably assured that, barring some accident, the patient with exophthalmic goiter would endure an uncomplicated partial thyroidectomy in one stage. And, so, in the field of colon surgery, only in recent years, since the advent of chemotherapy, could the surgeon be reasonably confident that the patient with carcinoma of the colon or rectum would survive an uncomplicated operation for resection of the colon."

The most convincing experimental evidence of the usefulness of these drugs as an adjuvant in surgery of the bowel comes from a study which shows the difference in healing of the intestine following open suture. This study showed advanced healing in the treated animals by the fifth postoperative day while there was little evidence of healing, and active acute infection persisted, in the control animals which did not receive sulfasuxidine or sulfathalidine either before or after operation.

Conclusion

A brief summary is presented of the introduction of two new drugs and the subsequent five years of researches, clinical trials and observations made by numerous investigators in several fields of study which have given these additional adjuvants to advance medical science.

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CALLING ATTENTION TO:

December, 1945

1. Interesting Books: E. S. Russell's *Directiveness of Organic Activities* sounds good (Cambridge Press, 204 pp., $2, 1945). So does E. Huntington's *Mainsprings of Civilization* (Wiley, N.Y., 1945, 672 pp., $4.75). Ditto for N. Cousins' *Modern Man Is Obsolete* (Viking, N.Y., 1945, 59 pp., $1). Also ditto for A. L. Kroeber's *Configurations of Culture Growth* (Univ. California, Berkeley, 1945, 832 pp., $7.50). And B. D. Panth's *Consider the Calendar* (Columbia, N.Y., 1945, $1.25). Also A. H. Leighton's *The Governing of Men* (Princeton Press, 1945, 420 pp., $3.75). Be sure to read C. L. Becker's Cook Lectures at Michigan: *Freedom and Responsibility in the American Way of Life* is a pertinent last testament applicable to us all (Knopf, N.Y., 1945, xlii and 121 pp., $2.50). R. B. Perry's *One World in the Making* offers worthy challenge (Current Books, N.Y., $5, 275 pp., $3.00). B. Russell pot-boils vigorously in *A History of Western Philisophy* (Simon Schuster, N.Y., 1945, 895 pp., $5.00). I. S. Kleiner's *Human Biochemistry* is welcomely concise (Mosby, St. Louis, 1945, 573 pp., $6.00). H. H. deJong discusses *Experimental Catatonia: A General Reaction-Form of the Central Nervous System* (Williams and Wilkins, Baltimore, 1945, 225 pp., $4.00). Williams and Wilkins also offer W. J. Hamilton, J. D. Boyd, and H. W. Mossman's *Human Embryology: Prenatal Development of Form and Function* (Baltimore, 1945, 366 pp., $7.00) L. E. Hinsie psychosomaticizes in *The Person in the Body* (Norton, N.Y., 1945, 263 pp., $2.75). J. G. Horsfall's *Fungicides and Their Action* should be useful (Chronica Botanica, Waltham, 1945, 239 pp., $5.00). Important is J. Felsen's *Dysentery, Colitis, and Enteritis* (Saunders, Philadelphia, 5, 1945, 618 pp., $6.00). Surgeons and obstetricians should welcome I. Chavez's *Enfermedades del corazon: Cirugia y embarazo* (Colegio nacional, Mexico, D.F., 1945, 182 pp.). Appropriate to the Roentgen centennial and to X-ray semi-centennial is O. Glasser's *Dr. W. C. Roentgen* (Thomas, Springfield, 1945, $4.50). C. C. Thomas also issues J. Adriani's *Chemistry of Anesthesia* (Springfield, 1945, $7). Watch for C. C. Thomas's *American Lecture Series.* Worthy text is E. Altenburg's *Genetics* (Holt, N.Y., 1945, 452 pp., $3.20. F. C. Waite well tells *The Story of a Country Medical College: A History of the Clinical School of Medicine, Woodstock, Vermont, 1827–1856* (Vermont Hist. Soc., Montpelier, 1945, 213 pp., $4.50). O. A. Bogomolets' *Influence of A.C.S. on Healing of Fractures* offers English summaries, as do most current Russian medical books (Kiev, Acad. Sci. U.K., U.S.S.R., 1944, 195 pp.). Provocative is G. K. Khrushchov's *Role of leucocytes in Reparative Processes of Tissues* (Moscow Academy, 1945, 116 pp.) Finally ready for distribution is *The Manual of the M. D. Anderson Hospital for Cancer Research,* and it's well done (Houston, 1945,

201 pp.). D. Guthrie offers a short *History of Medicine* (Nelson, London, 1945, 448 pp., 30s).

2. ANTIBIOTICS: Sir Howard (Nobelate) Florey's Lister Lecture to Royal College of Surgeons on October 11 well reviews history of antibiotics (*Lancet*, 2:503, Oct. 20, 1945). E. E. Hays and large St. Louis company confirm C. Bouchard's observation of antibiotics (*Compt. rend. Acad.*, 108: 713, 1889) from Pseudomonas aeruginosa (B. pyocyaneus) and obtain them in crystalline, potent, and nontoxic form (*J. Biol. Chem.*, 159:725, 1945). Merck's N. G. Brink and Co. offer interesting data on chemical relations of streptomycin (*Science*, 102:506, Nov. 16, 1945).

3. INTERESTINGS: J. Barcroft introduces symposium report on iodinated proteins (*J. Endocrin*, 4:219–370, 1945). E. J. Carey and Co. continue studies on nerve endings, reporting traumatic shock effects (*Amer. J. Path.*, 21:935, 72 plates, 1945). E. Shorr & Co. report on vascular agents in shock (*Science*, 102:489–498, Nov. 16, 1945). M. Spiegel–Adolf & Co. suggest breakdown of nuclear substances from electric convulsions (*J. Neuropath.*, 4:277, 1945). E. S. deLustig and E. Montnori find cardio-regulatory agent in embryonic myocardium similar to that localized in nodal tissue of adult heart (*Rev. Soc. Argentina Biol.*, 12:187–201, 1945). R. N. Lyons indicates vitamine K may be functional part of thrombin molecule (*Austral. J. Exp. Biol. Med. Sci.*, 23:131, 1945). T. and J. Gillman describe liver aspiration biopsy technic (*S. Afr. J. Med. Sci.*, 10:53, 1945). A. S. Wiener offers theory and nomenclature of Hr blood factors (*Science*, 102:479, Nov. 9, 1945). J. H. Gaddum wisely discusses lognormal distributions (*Nature*, 156:463, Oct. 20, 1945). J. F. Danielli well notes E. K. Rideal's Liversidge Lecture on biological significance of reactions at interfaces (*Ibid.*, 468). E. J. Conway & Co. (Dublin) offer new theory of gastric HCl formation (*Ibid.*, 477). G. E. Glock finds thiourea compounds produce adrenal cortex deficiency (*Ibid.*, 508, Oct. 27, 1945). Just arrived is E. A. Pequeno's remarkable auto-observation of five years experimental infection with treponema carateum, causing "pinto" (*An Inst. Invest. Cient. Univ. Nuevo Leon, Monterrey*, 1:17–72, 1944). J. T. Chesterman and W. J. Sheehan show statistically significant effect of morphine in preventing post-operative ileus (*B. M. J.*, 2:528, Oct. 20, 1945). Our own E. L. Porter and A. N. Taylor discuss facilitation of flexion reflex in relation to causalgia (*J. Neurophysiol.*, 8:289, 1945). And our R. F. Blount shows interrelationship of parts of hypophysis in development (*J. Exp. Zool.*, 100:79, 1945).

JANUARY, 1946

1. JOURNALS OF THE YEAR: American Geriatrics Society announces *Geriatrics*, published by *Modern Medicine*, Minneapolis. So, C. C. Thomas, Springfield, Ill., offers *Journal of Gerontology*, edited by R. A. Moore, at $6.00 yearly, with $3.00 for annual nontechnical supplement. B. Schwabe, Basel, Switzerland, announces that *Helvetica Medica Acta* will forthwith be joined by new *Helvetica Chirurgica Acta* and *Helvetica Paediatrica*

Acta, six issues yearly at 42 Sw. Fr. each. Academic Press, N.Y., offers *Journal of Colloid Science*, edited by V. K. LaMer, at $10.00. Schuman's, 20 E. 70, N.Y. 21, sponsors *Journal of the History of Medicine and Allied Sciences*, at $7.50, edited by G. Rosen, with interesting articles by C. Singer, J. C. Trent, G. Urdang, J. B. and C. M. Saunders, P. I. Nixon & Co. S. R. Detwiler gives well deserved tribute to grand old editorial board of *The Journal of Experimental Zoology* (*Science*, 102:610, Dec. 14, 1945). English physiologists offer helpful suggestions to authors (Ed. Bd., *J. Physiol.*, 104:221, 1945).

2. Reviews and Symposia: Note G. W. Beadle's keen survey of biochemical genetics, including data on cancer (*Chem. Rev.*, 37:15, 1945). W. B. Cannon and R. M. Field well review international relations in science (*Chron. Bot.*, 9:253, 1945). A. F. Barena summarizes data on ocular onchocerciasis (*Arch. Aso. evit. Ceg., Mexico*, 3:49, 1945). B. A. McSwiney's Penser Lecture covers visceral sensation (*Irish J. Med. Sci.*, 6th ser., No. 239, Nov., 1945). J. N. Davidson's fine Gillespie Lecture is on nucleoproteins in growth and development (*Edin. Med. J.*, 52:344, 1945). Sir Howard Florey's Lister Lecture on use of microorganisms for therapeutic purposes appears (*Brit. Med. J.*, 2:635, Nov. 10, 1945). A. Ritter reviews use of catgut sutures (*Helv. Med. Acta, Suppl.* 15, 1945). English authorities give comprehensive symposium on dermatology (*Brit. Med. Bull.*, 3:158–197, 1945). Forty-two friends of I. Chavez offer valuable contributions on cardiology in honor of his 25 professional years (*Libro Homenaje al Prof. Dr. Ignacio Chavez*, Nat. Univ., Mexico, 1945). W. B. Bean reviews cutaneous vascular "spider" (*Med.*, 24:243, 1945).

3. Histamine: W. J. Kerr & Co. report histamine-like material in nasal secretions of "common cold" and allergic rhinitis (*Am. J. Physiol.*, 144:706, 1945). Mayo Clinic staff note value of new anti-histamine compound, p-dimethylamino-ethyl benzhydryl ether HCl, Parke-Davis, *Proc. Staff Meetings Mayo Clinic*, 20:417, Nov. 14, 1945). This is confirmed by our W. A. Selle.

4. Bal.: British Anti-Lewisite, effective heavy metal detoxicant, is finally revealed by R. A. Peters, L. L. Waters, and C. Stock as 2,3-dithiopropanal (*Science*, 102:601, Dec. 14, 1945; *Nature*, Nov. 24, 1945). Acting by competing with proteins for arsenic it prevents inhibition of enzyme systems by heavy metals and reactivates such poisoned enzymes. Although irritating and toxic it is clinically useful in heavy metal poisoning. How about cyanide?

5. Toward a Better New Year: Univ. of California Press offers *United Nations Charter and Accompanying Documents* (2 vols., $17.50). Commonwealth Fund publishes studies of N.Y. Academy of Medicine Committee on Medicine and the Changing Order; E. J. Stieglitz's *A Future for Preventive Medicine* is out (Commonwealth, 41 E. 57, N.Y. 22, 95 pp., $1.00). Princeton Press announces History of Ideas Series, of which B. N. Nelson's *Idea of Usury* and M. H. Nicolson's *Newton Demands the Muse* sound promising (resp.: 150 and 175 pp., $2.00 and $2.50).

6. Etc.: S. Mazza & Co. report studies on Chagas disease (*Pub. 69, Univ. Buenos Aires, Mis. Est. Patol. Reg. Argentina,* 1945). E. Singer further emphasizes intracellular oxidases in detoxication of bacterial toxins (*Austral. J. Exp. Biol. Med. Sci.,* 23:165, 171, 1945). J. Gillman & Co. find phrynoderma not due to vitamin A deficiency (*S. Afr. J. Med. Sci.,* 10:67, 1945). P. Yazigi & Co. discuss failure of anatomical repair in cirrhosis of liver (*Rev. Med. Chile,* 73:755, 1945). E. W. Page reports on dopa decarboxylase activity of human tissues (*Arch. Biochem.,* 8:145, 1945). R. C. Herrin and W. J. Meek demonstrate vomiting from afferent stimulation by intestinal distention (*Am. J. Physiol.,* 144:720, 1945). G. L. Engel & Co. continue quantitative E.E.G. studies, comparing anoxia, acute alcoholism and hypoglycemia (*J. Clin. Invest.,* 24:691, 1945). Our E. H. Frieden and C. N. Frazier find blood plasma enhances penicillin action (*J. Bact.,* 50:279, 1945). Our C. M. Pomerat notes inhibition of reticuloendothelial immune serum on growth of Walker rat sarcoma in vitro (*Cancer Res.,* 5:724, 1945). Our H. J. Ralston and A. N. Taylor observe streamline blood flow in arteries and indicate its importance in work of heart (*Am. J. Physiol.,* 144:706, 1945).

February, 1946

1. More on Journals: British Medical Association will publish *British Journal of Pharmacology and Chemotherapy,* edited by J. Gaddum, four issues yearly, at 25s. Better get! Current subscriptions and back files of Russian medical journals may be ordered from Mezhdunarodnaja Kniga, Kuznetski most. 18, Moskva, U.S.S.R., or from Four Continent Book Corp., 253 5th Ave., New York City, at following prices: *Acta Physicochemica,* $10.00; *Biochemistry,* $5.00; *Bulletin Experimental Biology and Medicine,* $5.00; *Clinical Medicine,* $5.00; *Hygiene and Sanitation,* $1.30; *Journal Microbiology, Epidemiology and Immunology,* $6.00; *Medical Parasitology,* $4.00; *Neuropathology and Psychiatry,* $6.00; *Ophthalmology,* $6.00; *Pediatrics,* $5.00; *Problems of Tuberculosis,* $5.00; *Problems of Neurosurgery,* $5.00; *Pharmacology and Toxicology,* $4.00; *Soviet Medicine,* $5.00; *Stomatology,* $3.00; and *Surgery,* $6.00. *Science* seems to have improved format and policy.

2. Special Reports: O.S.R.D. promises 2,500-page report on screening studies on antimalarials. Office of Medical Information issues O. Temkin's well organized *Report on the Medicinal Treatment of Filariasis Bancrofti* (Nat. Res. Counc., Washington, 1945, 69 pp.). Office of Publication Board, Department of Commerce, issues mimeo series on recent German work: F. J. Curtis & Co., *Pharmaceuticals and Insecticides at I. G. Farben Plants, Elberfeld and Leverkusen* (Off. Pub. Bd. Rep. P. B., 237, 1945, 127 pp., 75c); A. M. Horack & Co., same title for Hochst am Main (P.B., 241, 38 pp., 25c); K. C. Blanchard, *Evaluation of Antimalarials* (P.B., 246, 20 pp., 25c); I. C. Kleiderer & Co., *Supplementary Report on Elberfeld* (P.B., 248, 141 pp., $1.00); I. C. Kleiderer & Co., *Pharmaceutical Activities at Hochst am Main* (P.B., 981, 139 pp., 75c).

3. ENZYMES: S. J. Bach well reviews biological methylation (*Biol. Rev. Cambridge Philosoph. Soc.*, 20:158, 1945). A. L. Lehninger shows activation of fatty acid oxidation is specific function of adenosine triphosphate, sensitive to sulhydryl reagents, requiring free carboxyl group, and diphosphopyridine nucleotide as component of oxidase system (*J. Biol. Chem.*, 161:437, 1945). D. E. Green & Co. discuss transaminases and indicate pyridoxal phosphate as prosthetic group (*Ibid.*, p. 559). K. E. Paschkis & Co. observe inhibition of cytochrome oxidase by thiouracil and sulfonamides (*Proc. Soc. Exp. Biol. Med.*, 60:148, 1945).

4. CANCER: Thirty reports covering virus approach, carcinogenesis, enzymes, diet and chemotherapy appear in *Cancer Symposium* (A.A.A.S., Smithsonian Bldg., Washington 25, 333 pp., $4.00). D. T. Thomas discusses mutation of healthy to malignant cell (*Nature*, 156:738, Dec. 22, 1945). H. Ulrich warns against danger of leukemia among radiologists (*N.E. J. Med.*, 234:43, Jan. 10, 1945). B. Scharrer describes tumors from nerve section in insects (Proc. Soc. Exp. Biol. Med., 60:184, 1945).

5. INTERESTING: W. Shepard vigorously and intemperately criticizes V. Bush's *Science, the Endless Frontier* and Committee to Support the Bush Plan (*Science*, 103:65, Jan. 18, 1946). F. D. MacCallum and J. A. R. Miles offer experimental evidence that infective hepatitis is caused by bowel excreted virus (*Lancet*, 1:3, Jan. 5, 1946). H. Eagle shows spirochaeticidal action of acid substituted phenyl arsenoxides is influenced by proportion of ion and free acid with undissociated free acid more strongly bound by parasite (*J. Pharmacol. Exp. Therap.*, 85:265, 1945). H. Shay & Co. suggest alkyl sulfates as gastric mucigogues for peptic ulcer (*Science*, 103:50, Jan. 11, 1946). E. G. Williams and F. W. Oberst give detailed data on biological and psychological effects in cycle of morphine addiction (*Pub. Health Rep.*, 61:1, Jan. 4, 1946). F. Hawking grows plasmodia in tissue culture (*Trans. Roy. Soc. Trop. Med. Hyg.*, 39:245, 1945). R. A. Gortner, Jr., & Co. show sugars may increase tooth destroying properties of phosphoric, citric, and other acids (*Arch. Biochem.*, 8: 405, 1945). J. D. Stone and F. M. Burnet report iodine vapor 0.1 ppm. vol. of air destroys infectivity of influenza virus (*Austral. J. Exp. Biol. Med. Sci.*, 23:205, 1945). G. E. Cartwright & Co. suggest chronic infection anemia due to iron fixation in tissues involving reticulo-endothelial system (*Science*, 103: 72, Jan. 18, 1946). A. R. Behnke reviews absorption and elimination of body gases in relation to fat and water content and decompression sickness (*Med.*, 24:359, 381, 1945). Our A. Ruskin and P. Rockwell discuss influence of dose and volume on circulation time (*Proc. Soc. Exp. Biol. Med.*, 60:40, 1945). Our E. J. Poth, E. B. Fernandez, and G. Drager describe prevention of end-bulb neuromata in painful amputation stumps (*Ibid.*, p. 200). Our A. E. Hansen reviews disturbances of lipid metabolism in children (*Southern Med. J.*, 39:32, 1946).